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APPLIED PHARMACOLOGY OF THE SKIN IN THE OPHTHALMOLOGIST'S EVERYDAY PRACTICE

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The therapy of diseases of the skin is still considered an art by many, and it is certainly true that seldom in medicine must schematic therapeutic procedures be avoided and the patient's entire personality borne in mind as much as in the treatment of diseases of the skin. The eyelids are an especially delicate and sensitive region of the skin, the condition and reactivity of which must be well considered before measures are taken for the treatment of their diseases.

The healthy skin is characterized by a certain turgescence, elasticity and color, all of which are subject to regular changes with age. The surface of the skin is protected and lubricated by a thin waterproof coating, the product of the sebaceous glands, the sebum. Under normal conditions the emulsion of moisture (sweat) and fat (sebum) on the surface of the skin is such as to maintain proper turgescence and greasiness, while adequate perspiration is being secured at the same time. If this proper emulsion becomes disturbed the perspiration increases and the skin loses its proper humidity and becomes either "rough," if the fat is scarce, or "oily," if there is an overabundance of nonemulsified fat. As the development and the productivity of the sebaceous glands are controlled chiefly by the sex hormones, the glands also undergo regular changes with age, and so does the protective coating, the greasiness of the skin. For the proper care and appropriate treatment of the skin this fact is of paramount importance. It is the reason why the same application is not appropriate—even for similar purposes—for the greaseless skin of the infant, the withered skin of the aged and the oily skin of the adolescent.

In puberty the activity of the sebaceous glands is generally increased. If the increase is out of proportion the condition is called seborrhea and may lead to complications such as comedo and acne of the face and ciliary blepharitis of the lid margins, either with increased scaling and crust

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formation (blepharitis squamosa) or with suppuration of the follicles of the eyelashes and the adjacent sebaceous glands (blepharitis ulcerosa). The skin of the lids itself (in contradistinction to that of the lid margin) is poor in sebaceous glands. Seborrheic manifestations of the lids are therefore rarely encountered, and while comedos of the face, for example, are characteristic of adolescence, comedos of the lids are peculiar to advanced age (Csillag [1]). In advanced age, however, they are not so much the result of increased production as of impaired elimination of sebum due to atrophy of the muscles of the hair follicles and diminished elasticity of the skin. Similarly, isolated seborrhea of the meibomian glands as described, among others, by Gifford,[2] Cowper [3] and Krückmann [4] is a condition that, according to my experience, is found only in persons of middle or advanced age. Moreover, I have found that the patients suffer mostly from some circulatory disturbance. The increased production of sebum in elderly persons seems to be due, rather, to an impairment in circulation of the blood, asphyxia of the tissues being, aside from hormonal and nervous influences, one of the main stimulants of the sebaceous glands.

In this connection it may be mentioned that the meibomian glands, in contradistinction to the regular sebaceous glands, have no muscle fibers (musculi arrectores pilorum) attached to them. This fact may be taken into account when one is searching for causative factors of the isolated seborrhea or comedo of the meibomian glands.

Production of sebum is more abundant in the brunet type; dryness of the skin and of the eyelids especially, a condition called "status subeczematosus," with increased vulnerability to any external irritant (smoke, cosmetics, tears, conjunctival secretion), is more common in blond persons, especially of the female sex, and becomes more frequent with advancing years, but may be encountered in children with a fair complexion, their skin being extremely thin and of diminished resistance.

Exaggerated care in cleansing deprives the skin of its protective film, and so do wet, especially warm, compresses. But, peculiar as it may at first sound, water, by disturbing the physiologic emulsion of moisture in fat on the surface of the skin, desiccates the skin and favors its withering, and so does, of course, cleansing with soap, which removes the fatty protective film of the skin. Washing, cleansing and application of wet compresses, all everyday procedures which do not seem likely to produce

1. Csillag, J.: Neigung alternder Personen zur Bildung periorbitaler Komedonen, Dermat. Wchnschr. **88**:609, 1929.

2. Gifford, S. R.: Meibomian Glands in Chronic Blepharo-Conjunctivitis, Am. J. Ophth. **4**:489, 1921.

3. Cowper, H. W.: Meibomian Seborrhea, Am. J. Ophth. **5**:25, 1922. This paper gives a good account of the literature.

4. Krückmann, E.: Ueber die Seborrhöe und den Komedo der Meibomschen Drüsen, Arch. f. Augenh. **91**:167, 1922.

any damage, may thus well be the reason for a chronic irritation or redness of the lids and even for rhagades of the angles of the eyes or for an eczema of the lids.

Washing and cleansing are, nevertheless, the beginning of every dermatotherapy, and one should know how they are performed properly. Especially should the fact just mentioned, that water desiccates, be remembered. Thus, weeping lesions or an oily skin calls for wet applications. Dry lesions can be treated with such applications only if not too irritated and sometimes not at all.

THERAPEUTIC PROCEDURES

Washing.—In seborrheic conditions of the lid margins (blepharitis), it is useful to wash the lids with warm water and even to use a nonirritating soap. The water should preferably be softened by the addition of sodium borate or an infusion of matricaria (chamomile).[5] Washing with boric acid solution before the application of a disinfectant ointment (ammoniated mercury) is necessary in cases of impetigo. One should not, however, employ any sort of washing or compresses in the case of a dry eczema or any acute dermatitis of the lid, in the later stages of herpes zoster or in the case of fissures (rhagades) of the angles of the eye, generally caused by exaggerated care. Some patients, of course, feel badly about being advised against the use of water or some sort of an eyewash. In this event I suggest the use of lukewarm milk or a mixture of milk with an infusion of matricaria or with sodium borate solution.

Cleansing.—When the skin of the lids is dry, irritated, eczematous, inflamed or affected with rhagades, one should use some soothing oily substance for the removal of scales, crusts, desiccated secretions or previously applied ointments. A pledget soaked in olive oil, castor oil or liquid petrolatum is good; cod liver oil is probably the best for such purposes. For chronic inflammations of the lid margins of seborrheic persons one should, on the other hand, use some nongreasy, possibly fat-dissolving substance. A toothpick swab dipped in benzine,[6] tincture of iodine, hydrogen peroxide or silver nitrate solution is good for such cleansing. (The cotton has to be wound tightly around the toothpick or a small glass rod applicator and the superfluous fluid squeezed out so

5. The flower head of the so-called Hungarian or German chamomile (Matricaria chamomilla Linné) is official in many European pharmacopeias, and chamomile tea is one of the oldest popular medicines in Europe. It is an excellent ingredient for the softening of water and does not seem to be so well known in this country as it deserves to be. It is not listed in the Pharmacopeia of the United States but is mentioned in the National Formulary (ed. 6, p. 257) under the name "matricaria." It can be heartily recommended.

6. Benzine for cleansing has also been advised by Gifford (Gifford, S. R.: Ocular Therapeutics, ed. 2, Philadelphia, Lea & Febiger, 1937, p. 154).

that none gets into the eye.) Only if there is an inflammatory reaction accompanying a chronic seborrheic blepharitis (e. g. an incipient hordeolum causing a dermatitis of its vicinity) or crusts are so adherent as to need preparatory softening should one use some oily substance or petrolatum for cleansing in spite of the seborrhea. Then, however, one should remove the abundance of fat after the cleansing has been accomplished with one of the just mentioned nongreasy agents.

The question of cleansing in the case of chronic blepharitis will be dealt with later and only an example mentioned here which shows the importance of ascertaining the functional status of the sebaceous glands, the dryness or greasiness of the skin in general and of the eyelids especially, before therapeutic measures are inaugurated.

A seborrheic, anemic young man suffered from an ulcerous blepharitis for years and was treated, among other things, with the much used official rose water ointment, i. e. with a fatty emollient ointment. He was also advised to wash his eyes with milk rather than with water. Thus he was to use applications suited to soften, soothe and cleanse a dry and roughened skin, and his condition became worse. The proper treatment in this case was softening of the crusts with a petrolatum ointment, careful removal of the crusts daily for about a week and cauterization of the ulcers with a rather strong (5 per cent) silver nitrate solution every other day after the thorough cleansing was carried out. The ulcers healed in about ten days, so that it became sufficient to cleanse the lid margins with benzine only. A definite improvement could be noticed in the course of a treatment of a few weeks.

I had several other cases in which suitable cleansing in itself (adapted to the seborrheic or eczematous character, respectively, of the condition) was sufficient to relieve disturbing and disfiguring lesions of the lids or lid margins. I want to stress this fact, as I have never seen mentioned in any of the standard textbooks that for diseases of the lids therapeutic procedures should depend first and foremost on a consideration of the oiliness or dryness of the skin of the affected area, a fact known by almost every woman regularly using toilet articles but seemingly not to all ophthalmologists.

Use of Hot and Cold Applications.—Its great specific heat makes water the best heat regulator. Cold applications may be used to withdraw heat in the treatment of acute inflammatory conditions, and tepid or hot applications, on the other hand, as irritants in the treatment of chronic or subchronic lesions or when it is desirable to increase the intensity and efficiency of an inflammatory process. Naturally, heat can be applied also in dry form (e. g. an electric pad, a hot water bottle), when the dryness or the inflammation of the skin precludes any wet application, or in the form of a mealy poultice, as for hordeola. Hot wet applications are the means of choice when irritative seborrheic lesions of the lid margins or inflammation of the conjunctiva rather than lesions of the skin are to be treated. The skin of the lids of elderly persons or of

women with dry skin should be protected with a cold cream or oil before wet hot packs are applied.[7]

Application of hot water (for example, in the form of a bran poultice) according to Strebel [8] is the best measure against the itching of vernal catarrh or allergic edema of the lids.

In general water as such is not used for compresses, nor is it used as an eyewash. It is made bland or is medicated; i. e., ingredients are added to it to endow it, as the condition may necessitate, with antiseptic, astringent or soothing properties. For the ophthalmologist only a few solutions are of importance. Compresses of zinc sulfate solution 1:500 are used to great advantage in the treatment of angular blepharitis caused by diplococci. Ichthammol solution 1-2:100 may be used for blepharitis and for erysipelas. Sodium hyposulfite solution 1-2:100 has been advised for compresses in the treatment of periocular dermatitis due to hair dyes (Ereaux [9]).

Lipschütz,[10] Hosford and Hicks [11] and also Duke-Elder [12] have emphasized the importance of the p_H of eye lotions, and Duke-Elder is certainly right in pointing out that the usual saturated boric acid solution, owing to its acidity, is not the proper cleansing lotion for the alkaline conjunctiva.[13] One has to remember, however, that for the skin a slightly acid reaction is the physiologic one and that dermatologists lay increasing stress on maintaining what is called the "physiologic acidity coat" of the skin (Schade and Marchionini,[14] Perutz [15]). Thus, when water should be used for compresses or fomentations in cases of conjunctivitis, hordeolum, etc., in which the skin is otherwise normal, a boric acid solution is to be preferred. One has to remember that the pledgets used come into longer and more intimate contact with the skin of the lids

7. This procedure was advised by Carter more than seventy-five years ago (Carter, R. C.: On the Local Application of Hot and Cold Compresses in Ophthalmic Diseases, Ophth. Rev. **2**:126, 1866) in a paper that is still as worth while reading as at the time it was written.

8. Strebel, I.: Ueber allergiebedingte Lidödeme und ihre Ursachen, Klin. Monatsbl. f. Augenh. **97**:644, 1936.

9. Ereaux, L. P.: The Cosmetic Eye: A Periocular Dermatitis, Canad. M. A. J. **42**:364, 1940.

10. Lipschütz, H.: Ueber die Bedeutung der Wasserstoffionenkonzentration im Bindehautsack, Klin. Monatsbl. f. Augenh. **82**:763, 1929.

11. Hosford, G. H., and Hicks, A. M.: Hydrogen Ion Concentration of Tears, Arch. Ophth. **13**:14 (Jan.) 1935.

12. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1523.

13. Hosford and Hicks [11] found the p_H of the tears to be around 7.35. Feldman (Feldman, J. B.: p_H and Buffers in Relation to Ophthalmology, Arch. Ophth. **17**:797 [May] 1937) found its average values to be between 7 and 7.5.

14. Schade, H., and Marchionini, A.: Der Säuremantel der Haut, Klin. Wchnschr. **7**:12, 1928.

15. Perutz, A.: Allgemeine Therapie der Hautkrankheiten, Berlin, Julius Springer, 1930, pp. 4 and 41.

to which they are applied than with the conjunctiva itself, although the application may be intended to influence the latter. For an eyewash proper, however, to be used with an eye cup or a dropper and thus to be applied directly to the conjunctiva, one should use not boric acid solution but a solution in which the acidity is neutralized by an adequate amount of sodium borate (borax, sodium biborate, sodium borate and sodium tetraborate are synonyms, sodii boras being the official designation of this compound), which in solution gives an alkaline reaction, or more preferably the "alkaline buffer solution no. 1" of Gifford,[16] with a p_H of 7.6. Because of its tannic acid content I have for many years prescribed hamamelis water (witch hazel water) or optraex as an eyewash. Both are good astrigents and check the secretions of the conjunctiva. As hamamelis water contains about 15 per cent alcohol,[17] it has to be diluted. Duke-Elder [12] recommended it for use in a dilution of 1 : 8.

Use of Powders.—In connection with the daily care of the eyes and lids a few words may be said concerning a therapeutic agent which is used more in the daily care of the skin than in the treatment of cutaneous lesions: powder. There are powders which act mainly by adsorbing moisture from the structures to which they have been applied. This moisture then evaporates and by evaporating abstracts heat. Thus adsorbing powders have an antiphlogistic effect. Magnesium carbonate is one of the best powders for the purpose. Talcum and zinc oxide, on the other hand, have mainly a protective action.

A good powder contains a mixture of adsorbing and protecting ingredients, so that it may have manifold beneficent effects—dehydrating, cooling, protecting and covering the irritated skin. A powder containing zinc oxide has some astringent and disinfectant effect, while one to which some fatty ingredient (wool fat or spermaceti, 2 to 5 per cent) has been added lubricates a dry skin and makes the powder adhere to it. Calamine (zinc oxide and ferric oxide [18]) gives a powder a pinkish hue and makes it less conspicuous. Drugs may also be added to powders; ichthammol, for example, makes a powder a good cosmetic with therapeutic properties in cases of rosacea.

A powder is a simple and effective remedy when the skin of the lids is irritated, for instance after hot packs have been used extensively, a bandage has been worn over a long period or the lids have been painted with iodine, as before an operation. A powder may be used for the protection of the lesions in the vesicular stage of herpes zoster of the lids.

Sometimes one has to prescribe a fat-containing powder for purely cosmetic reasons; it conceals fairly well the wrinkles of withering skin or dilated veins in the skin of the eyelids. Powder must not be applied to

16. Gifford, S. R.: Reaction of Buffer Solution and of Ophthalmic Drugs, Arch. Ophth. **13**:78 (Jan.) 1935.

17. National Formulary, ed. 6, p. 52.

18. National Formulary,[17] p. 64.

oozing, weeping surfaces. It would stick together, forming an artificial crust, which would not only hamper elimination of secretions but retain bacteria and debris.

Use of Lotions.—The protecting and cooling effect of a powder can be enhanced when it is given in the form of a so-called protective lotion, consisting of powder and water. The water of the lotion evaporates more quickly than moisture that has first to be adsorbed from the skin, as is the case when a simple powder is applied; hence the antiphlogistic effect is achieved sooner and is more intensive. Glycerin is added to lessen the drying effect and make the powder more adherent. The popular calamine lotion [19] may be used to good effect in the treatment of cutaneous condition affecting the lids:

℞		Gm. or Cc.
	Calaminae praeparatae	
	Zinci oxidi	āā 2.0
	Glycerini	0.5
	Liq. calcii hydroxidi	q. s.
	Ad	25.0

A patient suffering from chronic discharging conjunctivitis had been operated on for frontal sinusitis and for several days had to wear a bandage which kept one eye covered. A severe dermatitis of the face and lids due to the impeded flow of the conjunctival secretion developed. I advised use of a protective lotion for its soothing and disinfecting effect, with good results. The condition subsided in a few days, and the lotion could be substituted by a paste, until in about ten days full restitution was achieved.

I used such a lotion in several cases of dermatitis of the lids following the use of a dye on the eyelashes and the eyebrows (to be discussed later), but only, of course, if the dermatitis did not become severe enough to break the skin and cause weeping lesions, under which circumstances a paste (to be discussed later) had to be prescribed and consultation with a dermatologist became advisable.

If impetigo contagiosa, which so often affects the lids of children, becomes eczematous, a disinfectant lotion is advisable (Lutz [20]):

℞		Gm. or Cc.
	Resorcini	0.2
	Ichthammolis	0.5-1.0
	Zinci oxidi	
	Talci	āā 1.5
	Alcoholi diluti	
	Aquae destillatae	āā
	Ad	10.0

19. National Formulary,[17] p. 250. If a denser protective coating is needed, the amount of the powders can, of course, be increased. However, an increase is seldom advisable for the lids.

20. Lutz, W.: Die auf das Auge uebergreifende Hautkrankheiten, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1932, vol. 7, p. 319.

An important advantage of lotions is that they make bandages superfluous; thus they can be applied to the skin of the lids in any case in which it needs a protecting application and in which bandaging of the eye is not feasible.

Lotions produce a covering that is easily removed, when necessary, with hot water, oil or cold cream.

Protective antiphlogistic lotions, it should be realized, belong to the category of "dry" applications and, as has already been pointed out, even need an addition of glycerin to reduce their exsiccating effect. Moreover, oil, for example olive oil, must sometimes be added to counteract this effect. It has already been emphasized, however, that it is only dry lesions that respond well to dry applications, while weeping surfaces must not be treated with them. Thus, lotions should be used on fresh lesions, in cases of early acute eczema, for herpes zoster and for acute dermatitis, but if the lids have already become excoriated, cracked or weeping, one must not use powders or heavy powder lotions for any of the protective allaying, antiphlogistic or cooling effects that are desired. Nor should ointments, which retard the flow of moisture and secretions (this aspect will be discussed later), be applied. Antiphlogistic effects, protection and soothing of the skin are, under such circumstances, achieved with cold creams, and the drainage of secretions secured if necessary with pastes.

Application of Cold Creams.—A "cold" cream [21] consists of a hydrophilous ointment base and water. According to Moncorps' [22] investigations, the fastest cooling effect is achieved with such creams as form an emulsion of fat in water, i. e. an emulsion in which fat is dispersed in water as the dispersion medium. (Milk is the best known example of such an emulsion.) Wool fat (adeps lanae), the purified hydrophilous fat of sheep wool, on the other hand, when mixed with water yields an emulsion of water dispersed in fat, each particle of water thus being surrounded by fat. In emulsions of this type the evaporation of the water—thus its immediate cooling effect—is greatly hampered. Slow decomposition, however, of some of these emulsions will gradually free their water, thus securing a prolonged cooling effect, while the fatty component at the same time exerts its lubricating and softening action on the horny layer of the epidermis. It is this prolonged lubricating and cooling effect that makes the so-called lanolin creams (containing hydrous wool fat) so well known and the most popular creams in the daily care of the skin, especially of dry skin.

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21. It would more appropriately be called "cooling" or "refrigerating" cream.

22. Moncorps, C.: Untersuchungen über die Pharmakologie und Pharmakodynamik von Salben und salbeninkorporierten Medikamenten, Arch. f. exper. Path. u. Pharmakol. **141**:25, 1919; Ziele, Wirkungsweisen und Leistungen dermatologischer Heilmethoden und Pharmaka, Jahresk. f. ärztl. Fortbild. (no. 8) **20**:1, 1929.

The official U. S. P. cold cream, rose water ointment (unguentum aquae rosae),[23] consists of:

Spermaceti	12.5	Gm.
White wax	12	Gm.
Expressed almond oil	56	Gm.
Sodium borate	0.5	Gm.
Rose water	5	cc.
Distilled water	14	cc.
Oil of rose	0.02	cc.

The hydrous ointment (unguentum aquosum) of the British Pharmacopeia, containing olive oil and white petrolatum (soft paraffin B. P.), is similar. These cold creams may be used in the daily care of the skin of the eyelids when it is found to be dry and withering, in order to make it softer and more elastic, or to soothe it or protect it from irritation (for instance before hot wet packs are applied to the eye).

Instead of a prepared emollient, one will occasionally prefer to prescribe a cold cream made with boric acid solution, as the essential oils contained in the former sometimes irritate the eye or the lids (Ereaux[9]) or are not well tolerated by an already irritated skin. One prescription is as follows:

		Gm. or Cc.
℞	Adipis lanae	
	Liq. acidi borici 2 per cent	āā 10.0
	Petrolati albi	5.0

Another preparation, the refrigerating cream of Siebert,[24] contains the astringent and slightly disinfectant solution of aluminum acetate (Burow's solution):

		Gm. or Cc.
℞	Liq. alumini acetatis	2.0
	Aquae destillatae	5.0
	Adipis lanae hydrosi[25]	
	Petrolati albi	āā 10.0

Use of Pastes.—Pastes are a mixture of powder and grease. While providing fat to be absorbed by the horny layer of the epidermis, as do ointments and creams, they are at the same time permeable and porous on account of the admixture of powder, so that secretions can

23. Pharmacopeia of the United States of America, ed. 11, 1936, p. 417. A reliable chemist will be able to prepare this cold cream, using a 2 per cent boric acid solution and leaving out the rose water and oil, which sometimes irritate the eye (compare the next prescription).

24. Siebert, C.: Grundsätze und Verfahren bei der Behandlung von Hautkrankheiten, in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 1.

25. Hydrous wool fat containing 25 to 30 per cent of water (Pharmacopeia,[23] p. 36).

be partially adsorbed while the skin is lubricated and protected by the fat and some moisture is retained. Thus a paste can be applied even when the surface of the skin is weeping and the application of either the fat or the powder in itself would be prohibited. Because of their porosity, pastes do not retain heat or considerable moisture and do not isolate the structures they cover. Thus they have no effect on the deeper layers of the skin and should not be applied when the resolution of deep or chronic lesions is to be achieved. They also have poor refrigerating qualities. Their great importance lies in the fact just mentioned, that they can be applied as a protective and lubricating cover to broken, weeping surfaces which, at the same time, they help in drying. The most commonly used powders which should be incorporated in pastes are zinc oxide, talcum, siliceous earth and, for special purposes to be discussed later, magnesium carbonate. Zinc oxide endows pastes with mildly antiseptic and astringent qualities; of course, medicaments which enhance or modify these qualities can also be incorporated.

I found most useful the application of pastes in cases in which the skin of the lids became macerated by constant epiphora. This condition may cause, especially in elderly persons with withered, dry and sensitive skin, an unsightly condition of the lids, with the skin oozing and reddened and the eyelashes stuck together and may result in scarring and eversion of the lacrimal point, or ectropion. It is known that this finally leads to a vicious circle, the ectropion making the lacrimation worse and the latter the dermatitis and the ectropion. Chronic conjunctivitis may lead to a similar condition.

In the initial stage the irritation of the skin can be cured completely by breaking the vicious circle through the production of a suitable layer on the affected skin to protect it against the constant lacrimation. This layer is achieved most easily by means of an eschar precipitated by a 5 per cent silver nitrate solution or the official U. S. P. (3 per cent) solution of hydrogen peroxide and the application of a layer of paste, i. e. of fat and powder, on top of the eschar. This layer should not be removed for the first few days; moreover, a new layer of paste should be applied on each of the following few days. When this starts to slough off, oil is useful in cleansing.

It has been my experience that the time-honored zinc oil of Lassar is still the best in cases of this type of irritation. The olive oil it contains is avidly taken up by the greaseless, fissured skin, while the zinc oxide acts as a mild astringent and antiseptic. It consists of:

	Gm.
Zinc oxide	6
Olive oil	4

In most cases I have found this paste to be even better when some coal tar preparation (e. g. ichthammol 0.5 Gm.) was added to increase its emollient and antiseptic effect and endow it with a slightly resorptive quality.

Pastes are much milder in their action than ointments; they irritate less. Thus one should prefer them to ointments when allergic cutaneous reactions (for example dermatitis venenata caused by a hair dye) are to be treated.

I well remember the following case:

A young woman, a physician, of very fair complexion, by using a dye for her poorly pigmented eyelashes acquired an acute inflammation of the lids. This was cured in a few days when she refrained from the use of water and a paste of zinc oxide was applied daily.

Probably the best known zinc paste is one introduced by Lassar:

℞		Gm.
	Zinci oxidi	
	Talci	
	Adipis lanae hydrosi	
	Petrolati albi	āā 10.0

The official zinc oxide ointment (unguentum zinci oxidi) U. S. P.[26] is composed of the following ingredients:

	Gm.
Zinc oxide	20
Liquid petrolatum	10
Wool fat	5
White wax	5
White petrolatum	60

Pastes used in the practice of dermatology generally contain too much powder and are too thick to be conveniently applied to the eyelids. Atkinson[27] is therefore right in prescribing the following formula for use on the lids several times a day in cases of eczema of the lids:

℞			
	Bismuthi subnitratis	40 grains	2.56 Gm.
	Ung. zinci oxidi		
	Adipis lanae hydrosi	āā ½ ounce	15.5 Gm.

A similar paste is recommended by this author for the treatment of the cutaneous lesions in herpes zoster.[28]

Use of Refrigerating Pastes.—When a fat with hygroscopic qualities (e. g. hydrous wool fat) is combined with powder and water is added, or cold cream (which has the quality of absorbing powder)

26. The Pharmacopeia of the United States of America, eleventh revision, 1937, supp. 1, p. 89.

27. Atkinson, D. T.: External Diseases of the Eye, ed. 2, Philadelphia, Lea & Febiger, 1937, p. 86.

28. Atkinson,[27] p. 89.

is used to take up the powder, a preparation is produced which has both the qualities of a refrigerating cream and those of a paste. The same effect can be achieved simply by combining a cold cream and a paste.

"Refrigerating pastes" may also be used in the practice of ophthalmology. A good example is Neisser's "ointment," recommended by Axenfeld in the treatment of chronic inflammation of the lid margins for its nonirritating, pleasantly cooling and mildly astringent qualities:

			Gm.
℞	Zinci oxidi		
	Bismuthi subnitratis	āā	0.3-1.0
	Unguenti aquae rosae		
	Cerati [29]	āā	10.0

R. O. Stein [30] expressed approval of the use of Neisser's ointment in places where one does not like to, or cannot, apply a bandage in spite of an existing inflammation of the skin. Such places are areas around the eyes affected with eczema or other dermatitis, especially if conjunctivitis is present. Further advantages of this preparation, according to Stein, are that it is not too greasy, can easily be removed and is not too conspicuous.

When the skin of a patient is sensitive to a cold cream of the rose water variety,[23] there is another way of preparing a nonirritating refrigerating paste. One replaces the zinc oxide with magnesium carbonate. The latter has the remarkable quality of adsorbing great quantities of water. When this hydrated powder is mixed with an oil agreeable to the skin, one has another excellent paste with refrigerating qualities:

			Gm. or Cc.
℞	Magnesii carbonatis		5.0
	Liq. acidi borici 2 per cent		
	Petrolati albi	āā	10.0

One other refrigerating paste may be mentioned, which is especially valuable in the treatment of fissures of the lid margins:

			Gm.
℞	Ichthammolis		0.1-0.15
	Zinci oxidi		
	Bismuthi subnitratis	āā	1.0
	Ung. aquae rosae		10.0

29. Ceratum U. S. P. is composed of 30 per cent white wax and 70 per cent benzoinated lard (Pharmacopeia,[23] p. 115). It cannot be mixed with water and is used to increase the consistency of Neisser's ointment.

30. Stein, R. O.: Die durch kosmetische Hautaffektionen bedingten Entstellungen des Gesichtes und ihre Behandlung, in Pohl, L.: Chirurgische und konservative Kosmetik des Gesichtes, Berlin, Urban & Schwarzenberg, 1931, p. 61.

Pastes can be applied to most irritable skins; slight oozing or weeping is no contraindication. When I am in any doubt as to the nature of a lesion of the lids and the best form of treatment to be applied, I resort to a paste, usually a refrigerating paste, which can do little harm.

"Dermatologists agree that it is better to know a few therapeutic agents well, rather than to have a smattering of many."[31] It is especially important for the ophthalmologist to bear this quotation in mind, since his experience in treating diseases of the skin is limited.

Among my cases in which the use of pastes has been successful are widely varying cases of chronic eczema of the lids caused by epiphora and of acute dermatitis of the lids following the use of hair or eyelash dyes; cases of acute eczema of the face and lids following acute rhinitis or conjunctivitis, mostly in elderly persons, or prolonged administration of atropine; cases of irritation and swelling of the lids in young women due to irritating cosmetics; cases of herpes zoster of the lids, and cases of fissures at the angles of the lids caused by hot packs, etc. Sometimes, of course, as in the case already mentioned of the young man in whom a dermatitis of the face and lids developed after the face and eye had been bandaged subsequent to a sinus operation, it was first necessary to apply for a few days a protective lotion and only after the first signs of the dermatitis subsided could a paste be used. The same course had to be followed in cases of herpes zoster of the lids and in a case of acute atropine eczema. In cases like that of a dentist with a chronic severe procaine dermatitis involving the lids and conjunctiva, treatment with pastes was, of course, only of symptomatic value, my recognition and the subsequent elimination of the causative agent being of greater importance.

Use of Ointments.—The last-mentioned paste, originally recommended by R. O. Stein,[30] contains, in addition to the more or less indifferent ingredients (the powder, on the one hand, and the fatty base, on the other, which together form what is called a paste), a further ingredient with a definite therapeutic effect, the drug ichthammol. A fatty base, however, containing some drug is what, in the strict sense of the word, is called an ointment. Without, now, considering its consistency, one could therefore call R. O. Stein's paste an ointment on account of the drug it contains. This circumstance is emphasized merely to show that the different pharmacologic categories are not as well defined as they may seem, from the present exposition, to the less experienced. It has been shown previously in this paper that combinations and transitions among the different categories of

31. Light, S. E.: Palliative Treatment of Acute Undiagnosed Skin Diseases, Northwest Med. **40**:92, 1941.

dermatologic applications can be produced to the advantage of the individual patient; how, for example, the refrigerating paste is a transition from a cold cream (fat and fluid) to a paste (fat and powder) and, as a matter of fact, also from these to a lotion (powder and fluid). Several other examples could be mentioned. The Pharmacopeia of the United States calls both rose water ointment (a cold cream) and zinc oxide ointment (a paste) an "ointment," thus using the designation in the broader sense of a soft and easily spread medium consisting of fats or fatlike substances, and makes the only distinction by designating as a "cerate" the mixture of benzoinated lard and white wax.[29] The classification is rendered unclear by the further consideration that most authors call "pastes" only such fat-powder compounds as contain a percentage of powder high enough to give a pastelike, doughy consistency. Peter's well known ichthyol zinc ointment for the treatment of rosacea of the eye may be mentioned at this point as a good example of a transition from ointment to paste:

		Gm.
℞	Ichthammolis	0.15
	Zinci oxidi	0.50
	Petrolati albi	15.00

An ointment in the strict sense consists of a semiliquid or viscous, base and a drug.

Ointments are a therapeutic means familiar to every ophthalmologist. They are used routinely for the treatment of inflammations of the lid margins or for introducing drugs into the conjunctival sac. In the practice of ophthalmology, ointments as vehicles for therapeutic agents have been applied with the idea of prolonging and intensifying the therapeutic effect. Most ophthalmologists use ready-made ointments without caring or realizing in what sort of an ointment base the drug they intend to administer is incorporated, and their aforementioned effect is taken for granted. As long as only ready-made ointments are used, the expert knowledge of the manufacturer can be relied on in many cases. Proprietary preparations have successfully supplanted individually dispensed medicines, which, aside from many a beneficial effect, certainly has had the effect of greatly diminishing the art of dispensing and the general knowledge of pharmacodynamics. A certain amount of knowledge, however, is indispensable, and it will therefore be warranted to give some data relating to the properties of ointments and the demands that have to be made on ointments in order that they be of use and suited for the purpose one has in mind when prescribing them.

I shall consider only the problem of the ointment base, as the action of the drugs incorporated must be anticipated clearly by the dispensing

physician, and a discussion of their pharmacology would be outside the scope of this paper.

The problem of the ointment base is one of the oldest and most attractive in applied pharmacology of the skin. Before the advent of the manufacturing age only "natural," or organic, substances were used as the bases of ointments. Their use is as old as medicine. Lard, suet, olive oil, almond oil, butter,[32] spermaceti and wax, all time-honored ointment bases, had the great advantage of affinity with the human skin, and though their preparation would by no means have complied with modern hygienic demands, and their application was governed by superstition rather than by knowledge, their use was based on prolonged, though unsystematic experience. With the increasing knowledge of hygiene and skill in manufacturing chemical products, these natural fats have been supplanted by "fatlike" substances derived from inorganic sources, and the petrolatums came into general use as being more hygienic, more "neutral" ointment bases.

True, the first requirement of an ointment is that it be nonirritating, and this is usually (but not always!) well fulfilled by the petrolatums. They are also stable, while the classic ointment bases, such as lard and oil, become rancid only too easily and become irritating and repulsive. However, there is another requirement made on an ointment base, that it (1) take up the drug to be incorporated in it and (2) pass it on to the structures to which it has been applied. This is a highly complicated problem of colloid chemistry and has not yet been solved satisfactorily in relation to most ophthalmic ointments. Pure petrolatums cannot be mixed with water; thus water-soluble drugs cannot be applied in them. Von Liebermann,[33] one of the greatest experts in ocular therapeutics, emphasized in 1926 that ointments which do not form an emulsion with the tears (and the petrolatum ointments belong among these) are not suited as bases for drugs that are to be introduced into the conjunctival sac.

A further occasional requirement on an ointment, namely that the ointment base itself be taken up by the skin, cannot, of course, be fulfilled by any of the petrolatums. This is probably why, since the daily care of the skin (an art so highly developed by the ancient Orientals and Romans) has again come into its own, the natural fats have

32. A mixture of butter and cocoa or of spermaceti and wax with almond oil was the original base of Pagenstecher's famous yellow mercuric oxide ointment (Pagenstecher, A.: The Yellow Amorphous Oxide of Mercury and Its Application in Conjunctivitis and Corneitis Phlyctenulosa, Ophth. Rev. **2**:115, 1866).

33. von Liebermann, L.: Ueber Augensalben, Med. Klin. **22**:1216, 1926.

regained some of their importance in the therapeutics of the skin, especially since wool fat, the substance most closely akin to human sebum, was introduced by Liebreich into dermatology. Wool fat, and especially the more pliable hydrous wool fat,[25] is absorbed by the human epidermis (Unna and Fey [34]) and has become, rightly, the most important ingredient of ointments to be applied to dry skin. Another equally important quality of wool fat is that, owing to its cholesterol content, it forms an emulsion with water and watery solutions without any further preparation, thus fulfilling another of the most important requirements on ointment bases. This faculty makes hydrous wool fat the natural base for the incorporation of any water-soluble drug and is also the reason why this fat is now added to almost every petrolatum base. It is the addition of wool fat that makes the petrolatums suitable for carrying drugs which as a rule are insoluble in them [35]; and, as a matter of fact, the commonly used ophthalmic ointments now generally contain hydrous wool fat to absorb a watery solution of the drug which is to be incorporated. However, the problem of the administration of drugs in ointments is not yet solved. It has been shown by Bernhardt and Strauch,[36] Moncorps [22] and Klein and Scheffer [37] that when water is taken up by wool fat an emulsion of water in the fatty base is in most cases formed, which means that droplets of water are dispersed in and surrounded by a continuous medium of fat.[38] Such an emulsion has no electric conductivity, has a poor refrigerating effect [39] and, as shown by the remarkable experi-

34. Unna, E., and Fey, W.: Resorbiert die Oberhaut Fettstoffe? Dermat. Wchnschr. **88**:327, 1929.

35. The same effect can be achieved by the addition of an emulsifying agent, for example metacholesterol, to petrolatum, as is the case with vaselinum cholesterinatum of the newest Hungarian Pharmacopeia. Several ointment bases of this type are available in the United States.

36. Bernhardt, H., and Strauch, C. B.: Die Oel-Wasser- und die Wasser-Oel-Emulsionen in ihrer Beziehung zur Medizin, Ztschr. f. klin. Med. **104**:723, 1926. Strauch, C. B.: Ueber die Bedingungen der Aufnahme und Abgabe von Wasser oder Medikamenten durch Salbengrundlagen, Beitr. z. klin. Chir. **141**:358, 1927.

37. Klein, M., and Scheffer, L.: Experimentelle Untersuchungen am Auge ueber die Resorption aus Salben, Arch. f. Ophth. **128**:460, 1932.

38. In the papers by Unna and Fey,[34] Bernhardt and Strauch,[36] Moncorps [22] and Klein and Scheffer,[37] beautiful photomicrographs demonstrate this fact.

39. It has already been shown in this paper (page 966) that this holds true only as long as the emulsion is stable, while, on the other hand, through the slow decomposition of such an emulsion the dissolved drug may gradually become liberated, a prolonged action thus being secured. This is the advantage of rose water ointment (Moncorps,[22] p. 38) and of the ointment base consisting of petrolatum and hydrous wool fat in equal parts (Moncorps,[22] p. 36-37), official in the German Pharmacopeia as unguentum molle (Deutsches Arzneibuch, ed. 6, 1936, p. 742). It is the base of the refrigerating cream of Siebert [24] (see page 967 of this paper).

ments by Klein and Scheffer, is unable to communicate a drug dissolved in the droplets of water to the structure to which it has been applied. These authors applied a solution of sodium iodide in different ointments to the corneas of rabbits and determined by a micromethod the amount of iodine taken up by the cornea and the anterior chamber. They arrived at the astounding result that no iodine penetrates the eyeball from a petrolatum–hydrous wool fat base. When a soap, potassium oleate, was used as the emulsifying agent, an emulsion of the petrolatum was formed in the watery solution as the continuous phase, and iodine could be found to enter the eye in abundance. Of course, these experimental data cannot yet be generalized; they indicate, however, that whether the usual petrolatum–wool fat bases or other possible emulsions are best suited to carry different water-soluble drugs, especially to the eye, is a question which is to be investigated systematically for each drug and not to be taken for granted because of the manufacturers' statements, while so far as such qualities as blandness, equality of distribution and stability are concerned, these ointments may, in fact, be excellent.[40]

Pure petrolatums furnish bland and indifferent protective agents; they seclude the skin from the environment [41] and retain the moisture and the heat of the skin itself. They impede perspiration and act like an impermeable bandage,[42] loosening the structure of the epidermis and making possible the penetration into the depth of the skin of certain incorporated medicines (e. g., salicylic acid, Moncorps [22]). While this means that no petrolatum ointment should be used in any case of acute dermatitis in the treatment of chronic lesions, such as rosacea of the lid margin or of the conjunctiva, when the purpose of medication is (1) to increase inflammatory processes that have become chronic and inefficient and (2) to cause a drug (such as ichthammol) to exert a resolving influence on deeper than epidermal lesions, a petrolatum ointment is the most appropriate. Peters' ointment, mentioned previously, with its ichthammol content, belongs to this class. Being rendered slightly milder by the addition of some zinc oxide, it is the best preparation for the treatment of rosacea of the lids and the eye (Triebenstein,[43] von Liebermann [33]).

40. I am confident that an investigation of these problems conducted under the auspices of the manufacturers, on the one hand, and the competent ophthalmologic societies, on the other, by biochemists and ophthalmologists would be of great value. The study of a new type of ointment bases, called "wetting agents," should prove especially promising in this connection.

41. This is the reason why workmen in certain chemical industries have to rub their hands with petrolatum for protection before going to work.

42. Covering the lids with boric acid ointment after an intrabulbar operation converts the conjunctival sac into a wet chamber, which is considered beneficial.

43. Triebenstein, O.: Die Rosaceaerkrankungen des Auges, Klin. Monatsbl. f. Augenh. **68**:3, 1922.

For the treatment of inflammation of the lid margins in the wake of seborrhea (so-called blepharitis), petrolatum ointments are not the most desirable ones. Petrolatums lack porosity and clog the pores of the skin, hampering breathing and perspiration. Gifford [2] recommended zinc cerate in the treatment of seborrhea of the meibomian glands. Atkinson [27] advised a bismuth subnitrate paste in the treatment of blepharitis. Krückmann [4] recommended its use for a condition which he designated as comedo of the meibomian glands. Liebermann [44] had recommended in 1912 the use of a bismuth compound (tetrabrompyrocatechin bismuth [noviform]) for the treatment of chronic blepharitis. It is a mild disinfectant and has a demulcent, drying and antiphlogistic effect.[45] In a pure petrolatum base it, too, may of course become irritating.

No expert in the treatment of blepharitis will overlook mentioning that blepharitis cannot be cured simply by applying an ointment.[46] The nonspecialist, particularly, relies too much on ointment; he likes to prescribe yellow mercuric oxide ointment for almost every type of external disease of the eyes coming under his observation, which is wrong. Mercuric oxide is good only for phlyctenular keratoconjunctivitis,[47] while ammoniated mercury ointment is excellent in the treatment of impetiginous lesions of the face and lids, such as blepharitis ulcerosa and external hordeolum and for the treatment of allergic dermatitis following the use of hair dyes. Ointments for the treatment of chronic blepharitis, as has already been mentioned, should contain zinc oxide, bismuth or ichthammol, not mercury.

Mechanical cleansing, however, as I have repeatedly emphasized,[48] is the first and foremost therapeutic procedure in the treatment of chronic blepharitis, regardless of whether it is of the scaling, crust-forming or ulcerous type. This cleansing should be performed daily and by the physician himself, a fine toothless forceps, a small sharp curet and a wisp

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44. von Liebermann, L.: Zur Therapie der Lidrandentzündungen, Deutsche med. Wchnschr. **38**:512, 1912.

45. Noviform is not sufficiently well known in this country. I know of only one firm (Manhattan Eye Salve Co., Louisville, Ky.), which has a noviform ointment on its list.

46. Aside from the works of Liebermann, Gifford and Atkinson already quoted, see also McCool, J. L.: Diseases of the Eyelids, in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 348.

47. This is also Duke-Elder's opinion.[12] Moreover, it is this condition for which mercuric oxide was originally recommended by Pagenstecher. Hosford and McKenney also called attention to the frequent misuse of yellow mercuric oxide ointment (Hosford, G. N., and McKenney, J. P.: Ointment of Yellow Mercuric Oxide [Pagenstecher's Ointment], J. A. M. A. **100**:17 [Jan. 7] 1933).

48. Linksz, A.: Dermatotherapie in der alltäglichen Praxis des Augenarztes, Klin. Monatsbl. f. Augenh. **98**:435, 1937; Treatment of Blepharitis and Seborrhea of the Lid, Therapia, Budapest, 1937, no. 8.

of cotton on a glass rod or toothpick dipped in an astringent solution (2 to 5 per cent silver nitrate, 1 per cent zinc sulfate, 3 per cent hydrogen peroxide), being the necessary instruments. It may be a wearisome and tedious procedure; however, only after removal of the small scales and crusts, which are often hidden between or under the eyelashes and in the orifices of the follicles, can any therapeutic procedure be of benefit. Only after the most thorough cleansing will any applied ointment really reach, not the crusts or scales, but the structures which it is meant to attack.[49]

The mechanical cleansing is best done every day for a week or two. Fewer and fewer scales will have to be removed.

In the case of seborrhea of the meibomian glands, the cleansing must be done less vigorously. Usually there are no crusts. The frothy secretion of the lid margins can be removed with a boric acid (2 per cent) or resorcinol (0.25 per cent) solution or with a toothpick swab dipped in benzine. An excellent method of removing the accumulated secretion of the meibomian glands is massage of the eyelids by pressing them toward each other with the thumb of one hand and the index finger of the other or with the two thumbs (Selz,[50] Gifford,[51] Comberg [52]). It is amazing how much fatty, pussy or watery secretion can sometimes be removed from these glands by this method and how much relief the removal gives to some patients.

Use of Counterirritants.—As hyperkeratosis is one of the main pathologic anatomic characteristics of seborrhea, artificial desquamation of the epidermis is a standard method of treating this condition. Artificial desquamation is done with irritants, by the production of a dermatitis. It causes hyperemia and stimulates and revitalizes the tissues, like any other type of activating therapy. Of course, most of the so-called rubefacients, the counterirritants of pharmacology, are too irritating to be applied to the lid margins. However, there is one rubefacient which can be applied conveniently and with excellent results: tincture of iodine.

I generally use this in a concentration of about 3.5 per cent (half the strength of tincture of iodine U. S. P.[53]). On more delicate skins, the mild tincture of iodine U. S. P. (containing 2 per cent of iodine [53]) can be used.

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49. von Liebermann [44] cautioned against the use of a sharp instrument for cleansing in the treatment of ulcerous blepharitis. Bleeding from the ulcers may prevent the applied ointment from sticking to the skin; formation of a blood clot prevents it from penetrating into the skin and provides a welcome medium for the growth of bacteria.

50. Selz, E.: Beitrag zur Augenmassage, Ztschr. f. Augenh. **41**:272, 1919.

51. Gifford.[2] A photograph in this paper illustrates how the massage is done (p. 493). Similar photographs can be found in the two other papers mentioned.

52. Comberg, W.: Physikalische Therapie, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1932, vol. 7, p. 680.

53. Pharmacopeia of the United States,[26] 1939, supp. 2, p. 110.

Application to the lid margins, especially the orifices of the follicles, should be made every four or five days immediately after the mechanical cleansing has been completed. I paint the eyelashes themselves, their roots and the skin in their neighborhood thoroughly with tincture of iodine. If the wisp of cotton is wound tightly around the end of the glass or toothpick applicator, none of the iodine is likely to enter the conjunctival sac.

Touching the lids with tincture of iodine is followed by a more or less acute dermatitis involving the subcutaneous tissue, which lasts for a few days. After that the dry, sloughing epidermis of the lids and of the lid margins peels off in lamellas. The new epidermis under the peeling lamellas looks like the skin of the newly born; it has a fresh, pink color and is free from scales, and the orifices of the follicles are open and clean; smooth eyelashes, undefiled by secretion, are seen to originate from them.

If only the irritating, refreshing, rubefacient effect is desired, without desquamation, massage of the lids with any alcoholic toilet water, eau de cologne (for instance perfumed spirit N. F.), or undiluted hamamelis water (witch hazel water) is good.

REACTIONS TO DYES

A treatise on the dermatopharmacology of the eyes cannot be complete today without touching on the question of certain drugs applied to the eyelashes and eyebrows not for therapeutic but for cosmetic purposes and providing in some, fortunately exceptional, cases a serious problem due to the lesions they cause. I am speaking of dyes. An extensive literature may be found, mostly in nonophthalmologic magazines, on the damage caused by eyelash and eyebrow dyes. The interest and the experience of ophthalmologists seem to be restricted in this field. I know of only two recent papers in the American ophthalmologic literature [54] dealing with this question, which certainly deserves some attention, and a paper by Lillie [55] which gives an account of other cosmetics causing eye troubles.

The German ophthalmologist Bab [56] in the last fifteen years has reported on a number of cases of more or less severe lesions of the eyes due to eyelash and eyebrow dyes. Two papers in the Italian ophthal-

54. (*a*) Block, H. M.: Chemical Conjunctivitis Following Eyelash-Dyeing, Am. J. Ophth. **18**:1052, 1935. (*b*) Keschner, M., and Rosen, V. H.: Optic Neuritis Caused by a Coal Tar Hair Dye, Arch. Ophth. **25**:1020 (June) 1941.

55. Lillie, W. I.: Cosmetics Detrimental to Vision, Sight-Saving Rev. **6**:163, 1936.

56. Bab, W.: Schädigungen des Auges durch Schönheitspflege, Klin. Monatsbl. f. Augenh. **80**:665, 1928; Schädigung des Auges durch Wimpernfärbung, Deutsche med. Wchnschr. **59**:1041, 1933; Allergische Augenerkrankungen nach Dauerfärbung der Wimpern, Klin. Monatsbl. f. Augenh. **97**:391, 1936.

mologic literature (Sgrosso [57] and Neuschüler [58]) are known to me. I do not assert that this enumeration of the literature is complete.

There are two different ways of dyeing the eyelashes and eyebrows (as of dyeing the hair): (1) by physical and (2) by chemical means.

Physical methods ("coating" of the hair) as such are not dangerous. They consist in the application of a colored powder (e. g., lamp black, ivory black, graphite or india ink) in a fatty or acacia base. These dyes stick to the eyelashes and make them darker and longer. They can be easily removed. I have seen them cause blepharitis by blocking the follicles of the eyelashes if applied too close to their roots and an occasional infection (such as hordeolum) due probably to unclean handling. Such lesions have been reported by Bab.[56] Severe allergic or other lesions, however, have seemingly not been reported, and in my many years of practical experience, during which my patients have included a number of stage and screen actresses who applied coating substances professionally, I have never seen any considerable damage. So-called "coating" with salts of heavy metals, however, is dangerous.[59] A case reported by Schrader,[60] in which a dye containing copper salts caused ulceration of the skin in the region of the eyebrows, and 2 of Sgrosso's [57] cases may be mentioned as examples.

For the dyeing of poorly pigmented eyelashes and eyebrows, however, beauty shop operators usually resort to chemical methods of dyeing ("staining" of the hair); i. e., they apply such dyes as will undergo a chemical reaction with the hair proper and change its color permanently. Most of these dyes are aniline dyes or contain an amino compound. The bleaching of dark eyelashes or eyebrows is unusual; on the contrary, women with a fair complexion and poorly pigmented eyelashes endeavor to darken their eyelashes. Unfortunately these women have a more sensitive, thinner and drier skin, often with redness of the lids, chronic blepharoconjunctivitis, and are thus more liable to respond with unfavorable reactions to the dyeing.

The first serious case, one of retrobulbar neuritis due to an aniline dye, was reported by Berger [61] as far back as 1904. Reactions to dyes

57. Sgrosso, S.: Su alcune rare affezioni oculari da tintura per capelli, Arch. di ottal. **32**:545, 1925.

58. Neuschüler, I.: Blepharo-conguinctiviti allergiche da cosmetico, Boll. d'ocul. **13**:1098, 1934.

59. The expression "coating" is improperly used, especially by beauty shop operators, to describe the mode of action of the heavy metals. They undergo a chemical reaction with the sulfur of the hair and "stain" the cuticle of the hair permanently (Mayer, R. L.: Pudern, Schminken, Haarfärben, und ihre gesundheitlichen Schädigungen, Med. Klin. **26**:1619, 1930).

60. Schrader: Gesundheitsschädigungen durch Haarfärbemethoden, Deutsche med. Wchnschr. **55**:1267, 1929.

61. Berger, E.: Sehstörung in Folge der Anwendung eines anilinhaltigen Haarfärbemittels, Arch. f. Augenh. **50**:299, 1904.

of the paraphenylenediamine group may become serious in susceptible persons. The exceptionally severe reactions in the case of Moran [62] and of McCally, Farmer and Loomis,[63] in which "touching up" of the eyebrows and eyelids led to corneal ulceration with loss of serviceable vision in one and in both eyes, respectively, were caused by a dye in this group. There is a case in the recent literature in which application of a dye to the eyebrows and eyelashes led to most severe local and general reactions, resulting in death (Forbes and Blake [64]). The reason for the damage is allergy to the dye, more exactly to oxidation products of the dye (R. L. Mayer [65]). An analysis of the action of paraphenylenediamine was given by Goodman.[66]

In this connection it may be worth mentioning that in studying case histories I found mentioned by Block [54a] that his patient was "intolerant to homatropine," while in the case of Moran's [62] patient "atropine had been discontinued for some time, because of atropine poisoning." These circumstances may be simply a coincidence, but they suggest increased sensitivity of such patients to substances other than aniline dyes. Berger's [61] patient also suffered from menstrual edema of the lids; 1 of Semon's patients (his cases will be discussed later), from edema of the lids caused by sunburn. One of my patients suffered from menstrual disorders and another showed signs of the beginning of the menopause. Many of the patients reported on showed signs of increased sensitivity. Persons who happen to be allergic to dyes may suffer severe edema of the lids even if only the hair of the scalp, and not the eyelashes, is treated.

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62. Moran, C. T.: Bilateral Necrosis of the Cornea Following the Use of a Hair Dye on the Eyebrows and Lashes, J. A. M. A. **102**:286 (Jan. 27) 1934.

63. McCally, A. W.; Farmer, A. G., and Loomis, E. C.: Corneal Ulceration Following the Use of Lash-Lure, J. A. M. A. **101**:1560 (Nov. 11) 1933. Several other cases of dermatitis and eczema following the dyeing of eyelashes are found in the same volume: Greenbaum, S. S.: Dermatoconjunctivitis Due to Lash-Lure, Eyelash and Eyebrow Dye, ibid. **101**:363 (July 29) 1933. Harner, C. E.: Dermato-Ophthalmitis Due to the Eyelash Dye Lash-Lure, ibid. **101**:1558 (Nov. 11) 1933. Bourbon, O. P.: Severe Eye Symptoms Due to Dyeing of the Eyelashes, ibid. **101**: 1559 (Nov. 11) 1933. Jamieson, R. C.: Eyelash Dye (Lash-Lure) Dermatitis with Conjunctivitis, ibid. **101**:1560 (Nov. 11) 1933. One other case of involvement of the cornea is mentioned in the Report of the Bureau of Investigation of the American Medical Association (J. A. M. A. **101**:1016 [Sept. 23] 1933).

64. Forbes, S. B., and Blake, W. C.: Fatality Resulting from the Use of Lash-Lure on the Eyebrow and Eyelashes, J. A. M. A. **103**:1441 (Nov. 10) 1934.

65. Mayer, R. L.: Ueber die Hautüberempfindlichkeit gegen Körper von Chinonstruktur, Klin. Wchnschr. **7**:1958, 1928; Untersuchungen über die durch aromatische Amine bedingten gewerblichen Erkrankungen, Arch. f. Gewerbepath. u. Gewerbehyg. **1**:436, 1930. Study of this excellent monograph should be highly recommended to everybody interested in related problems.

66. Goodman, H.: Eyelash Dye: Ill Effects and Some Problems Evoked by Them, Arch. Dermat. & Syph. **32**:258 (Aug.) 1932.

Dyeing with henna, an ancient vegetable dye used in the Orient, has always been considered harmless. However, considerable reactions have been reported after dyeing of the eyelashes, or merely of the scalp, with what was alleged to be henna. Of course, the designation "henna" is not patented. Investigations of Bab [56] and of the Committee on Furs, Hair Dyes and Cosmetics, Section on Dermatology and Syphilology, American Medical Association [67] show that most hair dyes advertised as henna dyes contain negligible amounts of this dye and owe their effect to other, often harmful, ingredients.

When a reaction to any applied dye develops, a vasoconstrictor substance (epinephrine, ephedrine) should first be applied. Dermal lesions should be treated after the principles outlined previously in this paper. Bab [56] recommended tepid or cool compresses of physiologic solution of sodium chloride. In the opinion of many dermatologists, an ointment of ammoniated mercury is almost specific. One should begin with a preparation containing not more than 0.5 per cent, as the sensitivity of an acutely inflamed eyelid to any drug may be unexpectedly high. If it is well tolerated the concentration can be increased to 2 to 2.5 per cent. Valuable hints on treatment have been given by Ereaux.[9]

Not only the eyelashes, however, but the eyelids themselves may be tinted with more or less innocuous substances, from lamp black compositions to aniline dyes. Ereaux [9] enumerated them among the causative factors in producing periocular dermatitis. Semon [68] described 4 cases of "palpebritis" which he traced to and correlated with the use of dyes for eyelid shading. Though Semon's evaluation of these cases has been criticized by Ingram,[69] his paper is worth reading by those interested in the subject, as it will give them valuable information on some technical problems of the preparation of cosmetic dyes.

For curiosity's sake it may be mentioned that even a case of papulovesicular dermatitis of the eyelids due to rubber on an eyelash curler, sensitivity to rubber having been verified by a patch test, has been reported (Fox [70]).

It may appear from the data presented that the use of hair dyes, eyelash dyes and eyelid shadows is extremely dangerous. However, I agree with Dr. Goodman,[66] one of the foremost American authorities on cosmetic dermatology, that in comparison with the enormous dissemination [71] of the use of dyes, the number of reported injuries is extremely

67. Cole, H. N.: Injuries from Hair Dyes, Furs, Cosmetics, J. A. M. A. **88:** 397 (Feb. 5) 1927.

68. Semon, H. C.: Palpebritis from Eyelid "Shading," Lancet **2:**1267, 1936.

69. Ingram, J. T.: Dye-Dermatitis of Eyelids, Lancet **2:**1365, 1936.

70. Fox, E. C.: Dermatitis of the Eyelids Due to Rubber on an Eyelash Curler, Arch. Dermat. & Syph. **28:**222 (Aug.) 1933.

71. In Germany alone 10,000,000 packages of hair dye are sold annually (Lancet **2:**1281, 1936).

small. Nevertheless, caution is indicated and better legislation as to government control of manufacturing imperative.

Physical methods of dyeing the eyelashes, properly and cleanly carried out, are permissible. The use of heavy metals is forbidden in several European countries; it is dangerous. By introduction of the compulsory patch test most of the detrimental effects of aniline dyes will probably be eliminated. Aside from these effects, lesions of the cornea are due to improper handling rather than to allergic reactions. No dye must ever come in contact with the conjunctiva.

COMMENT AND SUMMARY

The most appropriate comment on the foregoing pages is the following quotation from one of the best known textbooks on pharmacology [72]:

> Whereas the healthy skin is a very resistant tissue and is not injured by the application of all kinds of powerful medicaments, diseased skin is, on the other hand, usually extremely sensitive and easily irritated. For this reason the treatment of skin diseases is concerned very largely with the use of protective and soothing substances and also with the use of substances which will produce any particular action desired, e. g. antisepsis, without irritating the skin.

It is shown in the present paper how these substances can be and should be applied to a region with special functions and of peculiar structure and great delicacy, viz., the eyelids. The presentation of methods of treatment is not given from the point of view of the etiology or of the pathology of diseases affecting the skin of the eyelids or the lid margins, but, as the title of the paper implies, from that of pharmacologic categories. Such a presentation is necessarily one sided and incomplete, no attempt having been made to enter into equally important problems of the causal or the general treatment of most of the diseases mentioned. To give but one example, disturbances of digestion or of endocrine functions or of both will be found in many cases of seborrhea or of rosacea of the lids, and general treatment (such as the administration of vitamins) will, therefore, certainly be of great benefit. Similarly, specific therapy of the causal bacterial agent, with toxoid or a sulfonamide compound, in many cases of chronic blepharitis, as recently recommended by Thygeson, may give better results than most of the local applications described in this paper. A consideration of such problems of etiology and therapy, however, would not have been in line with the aim of the paper, and both the pertinent literature and my experiences have therefore been purposely disregarded.

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72. Clark, A. J.: Applied Pharmacology, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1940.

PAPILLEDEMA IN GENERAL DISEASES

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The occurrence of a choked disk type of elevation of the nerve head in the course of a general disease has often led to difficulty and confusion in diagnosis. Examination of the fundus in these circumstances has led to the tentative diagnosis of brain tumor, but further investigation directed toward proving this has been in vain. However, since the spinal fluid pressure is often elevated, the neurologist or the neurosurgeon may be convinced that primary cerebral disease exists. The literature on the subject has been extensive, and the various opinions concerning the meaning of the elevation of the nerve head have been particularly well reviewed by Larsòn.[1] Case reports include Cushing and Bordley's [2] description of a case of nephritic neuroretinitis in which relief of the increased intracranial pressure by decompression resulted in improvement in the neuroretinitis. In 1924 Larson [1] reported 11 cases in which nephritic retinitis was accompanied by increased intracranial pressure. Fishberg and Oppenheimer [3] in 1930 acknowledged the presence of increased intracranial pressure in some but not in all cases of neuroretinitis. Koyanagi [4] (1935) published reports on 4 cases of nephritic neuroretinitis, in 2 of which there was increased intracranial pressure. Recently Watkins, Wagener and Brown,[5] in writing on choked disks in blood dyscrasias, referred to 4 cases in the literature and reported 2 of their own in which the intrathecal pressure was elevated. These reports offer adequate evidence that increased intracranial pressure is often an accompanying finding in neuroretinitis associated with general disease. In most instances no evidence of

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1. Larson, S. W.: Choked Disc in Nephritis, Acta ophth. **1**:193, 1924.

2. Cushing, H., and Bordley, J.: Subtemporal Decompression in a Case of Chronic Nephritis with Uremia, Am. J. M. Sc. **136**:484, 1908.

3. Fishberg, A. M., and Oppenheimer, B. S.: The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Diseases, Arch. Int. Med. **46**:901 (Dec.) 1930.

4. Koyanagi, Y.: Ueber die Entstehung der Stauungspapille bei Retinitis nephritica, Klin. Monatsbl. f. Augenh. **95**:182, 1935.

5. Watkins, C. H.; Wagener, H. P., and Brown, R. W.: Choked Discs in Types of Blood Dyscrasia, Am. J. Ophth. **24**:1374, 1941.

cerebral neoplasm can be obtained from clinical or postmortem examination, yet the appearances of the nerve head and the increased spinal fluid pressure remain as contradictory and confusing evidence. The increased pressure and the consequent swelling of the nerve head appear to be the result of changes in the brain tissue that occur as a manifestation of the general disease rather than as the effect of a primary neoplasm of the brain.

Unfortunately no definite information is available concerning the causation of the increased intracranial pressure in such cases. In some cases, hemorrhage, either in the ventricles or meningeal spaces or into the brain substance itself, may be responsible. Yet postmortem study of the brain frequently discloses no apparent hemorrhage or lesion. Watkins, Wagener and Brown have suggested that edema of the brain may be the underlying pathologic process; yet sufficient data is not available to substantiate this contention.

For further study of this subject, readings of the intrathecal pressure were made on a variety of patients in the medical wards of the University Hospitals. The patients were hospitalized for hypertensive vascular disease, nephritis, leukemia, anemia, diabetes and arteriosclerosis, and all had ophthalmoscopic evidences of the general disease. In some, however, there was definite papilledema, while in others the nerve heads were not edematous.

The results of these observations are shown in tables 1 and 2.

COMMENT

Among the hypertensive patients (table 1) we found a consistent relationship between the presence of papilledema and increased intracranial pressure, for all but 1 of the patients in this group had abnormal pressure (above 200 mm. of water). Although there is no direct relationship between the amount of pressure and the extent of the papilledema, in general the patients with the higher pressures had the greater amount of edema. The patient in the group with normal intrathecal pressure had a severe hypertensive retinitis with extensive edema of the entire posterior segment of the retina. It seems probable that in his case the edema of the nerve head was a component of the great edematous reaction of the retina to the general disease. If primary edema of the retina could exist it would explain the presence of a swollen nerve head without increased intracranial pressure. For the patients without papilledema the findings are consistent except for the patient in whom the pressure on admission was 300 mm. of water. During the late period of the disease edema of the nerve head did develop, however, and the spinal fluid pressure remained

elevated. This patient might be considered as one of the group with papilledema. The circumstances in his case may be similar to those in cases of cerebral neoplasm with hydrocephalus but without choked disks.

In the miscellaneous group of cases (table 2), we found that all the patients without papilledema had an intrathecal pressure of less than 200 mm. of water. Among the patients with papilledema there was only 1 in whom the intracranial pressure was within the normal limits.

TABLE 1.—*Hypertensive Vascular Disease*

Case	Name	Age	Blood Pressure	Papilledema	Intrathecal Pressure, Mm. of Water	
			Without Papilledema			
1	O. D.	31	190/130	—	180	
2	L. S.	44	290/130	—	135	
3	J. M.	66	220/120	—	140	
4	G. H.	45	190/126	—	130	
5	S. C.	45	226/155	—	163	
6	E. T.	41	174/100	—	140	
7	M. J.	54	220/120	*	189	
8	R. Y.	13	250/160	—	300 †	
			With Papilledema			
9	A. D.	46	210/112	+	300	
10	F. K.	52	230/150	+++	310	
11	A. W.	45	255/155	+	280	
12	T. K.	50	250/150	+++	335	
13	F. W.	52	192/138	+	242	
14	D. N.	48	220/130	++	285	
15	C. S.	52	220/120	++++	300	
16	D. L.	16	200/148	+	162	Diffuse retinal edema
17a	M. N.	17	245/190	+++	330	Papilledema disappeared after lumbar puncture and administration of hypertonic dextrose solution
17b	M. N.	1 mo. later	290/190	+++	390	
18	H. H.	45	250/150	+++	400+	
19	M. A.	37	204/140	+++	240	
20	P. W.	61	240/150	++++	216	Marked retinal edema

* Postmortem specimen showed ± edema.
† Before death choke developed.

This man (patient 32) had bilateral venous thrombosis and therefore would be expected to have edema of the nerve head because of the ocular condition itself.

Of the total of 17 patients with papilledema here reported on, 15 showed elevation of the intracranial pressure above the upper limits of normal. One of the patients without elevated pressure (patient 32) had no recognizable general disease, while the other had edema of the nerve head that was perhaps only a component of a generalized retinal edema. Despite the belief that an increased intracranial pressure exists in most patients with neuroretinitis, it seems highly probable that in

certain stages of general diseases a profound change in the physiology can result in edema of the retina and of the nerve head without a significant change in intrathecal pressure. This belief is augmented by the fact that in some cases a generalized retinal edema is most con-

TABLE 2.—*Miscellaneous Diseases*

Case	Name	Age	Diagnosis	Blood Pressure	Papilledema	Intrathecal Pressure, Mm. of Water
			Without Papilledema			
21	A. L.	58	Leukemic retinitis	144/ 78	—	110
22	A. W.	69	Anemic retinitis	110/ 44	—	130
23	A. A.	61	Addison's disease; arteriosclerosis	125/ 80	—	80
24	C. F.	18	Chronic nephritis	200/110	—	150
25	E. M.	33	Chronic nephritis	164/110	—	103
26	W. H.	62	Arteriosclerosis	140/ 80	—	80
27	M. A.	42	Diabetic retinitis	145/ 85	—	110
28	H. D.	51	Diabetic retinitis	160/ 88	—	135
			With Papilledema			
29	H. S.	42	Lymphatic leukemia	105/ 45	+	276
30	D. P.	19	Nephritic retinitis	150/ 90	++	270
31	M. M.	17	Nephritic retinitis	240/150	++++	500+
32	O. S.	53	Venous thrombosis (cause unknown)	145/ 95	++	150
33	J. F.	52	Leukemic retinitis	110/ 65	++	210

TABLE 3.—*Results of Postmortem Examination*

Case	Name	Brain Edema	Nerve Head Edema
7	M. J.	+	±
8	R. Y.	++++	++++
15	C. S.	+++	++++
16	D. L.	++	+++
17	M. N.	++++	Not obtained (+++*)
18	H. H.	+++	Not obtained (+++*)
21	A. L.	+	—
24	C. F.	+	Not obtained (death 2½ mo. after fundus report)
26	W. H.	+	—
30	D. P.	+++	++++
33	J. F.	+	++

* On ophthalmoscopic examination.

spicuous while in others the amount of involvement of the retina is slight in comparison with the swelling of the nerve head. In cases of the first sort the nerve head is elevated along with and because of the retinal edema, while in the latter cases the edema of the nerve head and that of the retina are primarily the result of increased intracranial pressure. Thus the existence of intrinsic retinal edema may explain the absence of increased intrathecal pressure in certain cases of neuroretinitis.

After lumbar puncture and drainage of cerebrospinal fluid the patient frequently has considerable improvement in his symptoms. Patient 17 was definitely improved temporarily after drainage of spinal fluid; the severe papilledema receded but gradually returned during the succeeding weeks. In other patients we had observed some decrease in the edema, but not to the extent that was seen in this patient.

The pathogenesis of the increased intrathecal pressure remains obscure. The possibility that a cerebral tumor is present has often been raised, yet postmortem evidence for this is entirely lacking. In patients who show intracranial hemorrhages at postmortem examination, it is probable that an increased pressure existed prior to the occurrence of bleeding. A rupture of a vessel in the meninges or in the brain substance may be only the terminal event superimposed on an already increased cerebrospinal fluid pressure. The pathologic material available in our cases showed no case in which there was a cerebral neoplasm and 1 in which cerebral hemorrhage at the base was the immediate cause of death, while in all cases there was some degree of edema of the brain. Although the number of cases is insufficient for the drawing of definite conclusions, the findings suggest that the edema is proportionate to the amount of increased pressure. The patients with particularly high pressures showed extensive edema of the brain substance, while those with lesser pressures showed little evidence of edema. In 3 patients in whom the intrathecal pressure was normal, microscopic evidence of edema was observed. The amount of edema may not have been sufficient to raise the intracranial pressure, or the mechanism for maintaining the pressure of the cerebrospinal fluid may have compensated for the swelling of the brain.

It is recognized that the cases presented show only the relationship between neuroretinitis and increased intracranial pressure. Just as choked disks do not develop in every patient with increased intrathecal pressure, all patients with increased intracranial pressure in association with general disease do not show neuroretinitis. Conversely, the neuroretinitis may be the result of purely local conditions in the retina, in which event the cerebrospinal pressure will not be elevated. The postmortem material suggests that edema of the brain is responsible for the increased intracranial pressure and that the degree of edema is reflected in the rise in pressure, which is indicated by the swelling of the nerve head.

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MULTIPLE SCLEROSIS AS AN ETIOLOGIC FACTOR IN RETROBULBAR NEURITIS

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Among the various causes of retrobulbar neuritis, demyelinating diseases of the brain and visual pathways play a most significant role. Prominent in the group of diseases classified as "encephalomyelopathies" is multiple sclerosis, a disease of unknown causation. In contrast to other causes of retrobulbar neuritis, it is characterized by recurrent episodes of symptoms and by remarkable variation in the intensity of disturbance of function in relation to the rapidity of onset of symptoms and to the degree of recovery from a number of episodes. Between attacks, the symptoms of which may be constitutional or local, the patient may experience no general, local or permanent effects. In the great majority of cases, multiple sclerosis begins with comparatively mild symptoms, from which recovery usually is complete. Subsequent attacks may not occur for a number of years.

Alpers [1] stated:

> The history of vertiginous attacks over widely scattered periods with what appear to be remission of the attacks may be interpreted as early episodes of multiple sclerosis. Where it is suspected as a cause of vertigo, it should be recalled that the classical, fully developed signs of multiple sclerosis may be and usually are absent, and that early signs of the disease . . . are much more likely to be found. It is a safe clinical rule that in obscure cases of vertigo, where a lesion of the brain stem is suspected, multiple sclerosis must always be considered.

Only a relatively few persons make incomplete recovery from the first attack of the disease, and the presence of multiple sclerosis, if it is suspected at all, could be only presumptive. As to the few who do not recover from the first episode, the disease they have is chronic, and subsequent attacks leave them still further incapacitated. In this small group the disease is readily diagnosed on the basis of symptoms and the characteristic laboratory observations.

When symptoms of numbness, paresthesia, dizziness and vertigo appear, followed by transient blindness and paralysis, multiple sclerosis may be presumed to have been responsible for earlier single symptoms.

From the Section on Ophthalmology, the Mayo Clinic.

Read before the Section of Ophthalmology, New York Academy of Medicine, March 16, 1942.

1. Alpers, B. J.: Vertigo: Its Neurological Features, Tr. Am. Acad. Ophth. **46**:38-54 (Nov.-Dec.) 1941.

such as scotoma and diplopia, which in themselves would not justify a diagnosis of multiple sclerosis. The early symptoms of multiple sclerosis, such as failing vision, paresthesia, a tingling sensation and numbness in the extremities, accompanied or preceded by dizziness, vomiting, general weakness and often mental or emotional instability, are suggestive of multiple sclerosis, but are not pathognomonic, since one or more of them are found in encephalomyelitis arising from other causes. Exogenous toxins such as lead, alcohol, tobacco, arsenic and other substances less frequently encountered also may produce one or more of the symptoms which characterize multiple sclerosis. Organic disease of the brain also must be considered.

Optic neuritis is a frequent complication of multiple sclerosis. Recovery from a mild first attack is the rule, and rarely is the patient made totally and permanently blind in both eyes. However, when the disease is fulminating and in all cases in which it is in the advanced stage, remissions of symptoms are incomplete, and response to treatment is discouraging. A carefully elicited history and a thorough physical and neurologic examination are essential to determination of what causes of blindness may be responsible in a given case of retrobulbar neuritis. Toxemias due to exogenous toxins such as lead, thallium, alcohol and tobacco; constitutional diseases, particularly diabetes and arteriosclerosis; peripheral vascular disease; brain tumor; arachnoiditis, and some other diseases of the central nervous system still are considered to be possible factors.

In a paper read before the Section of Ophthalmology of the New York Academy of Medicine in January 1933, I [2] called attention to the trend of current literature toward recognition of multiple sclerosis as being responsible for the greatest number of cases of retrobulbar neuritis. During the past ten years I think this trend has not diminished. Rather has there been a marked lessening of the trend toward the presumption that acute retrobulbar neuritis is due to disease of the paranasal sinuses. Now one rarely hears of acute retrobulbar neuritis being corrected by the surgical treatment of sinus disease. As a matter of fact, during the ten years that have elapsed since I discussed the subject of the relationship between sinus disease and retrobulbar neuritis, there has appeared at the Mayo Clinic not a single patient suffering from retrobulbar neuritis who has had recent acute sinus disease, nor has there been a single case of severe sinus disease associated with retrobulbar neuritis.

By a process of elimination of all other probable causes, when the characteristic scotoma can be demonstrated, retrobulbar neuritis often is attributed to multiple sclerosis as an early episode of that disease. Some cases of retrobulbar neuritis have been placed in the category of multiple sclerosis on evidence insufficient to establish that diagnosis, but

2. Benedict, W. L.: Retrobulbar Neuritis and Diseases of the Nasal Accessory Sinuses, Arch. Ophth. **9**:893-906 (June) 1933.

since the early symptoms of multiple sclerosis are often followed by other unmistakable signs of the disease, and since multiple sclerosis has been proved to be the cause of scotoma in a large number of cases of optic neuritis, particularly the retrobulbar type, the placing in that category of cases of early symptoms may be justified.

EARLY SYMPTOMS OF MULTIPLE SCLEROSIS

The early symptoms of multiple sclerosis to which attention should be directed when the history of a patient is being elicited are transitory muscular and sensory changes that affect particularly the extremities or the eyes. Among the ocular symptoms, diplopia and scotoma are outstanding. Disturbance of vision was given as the first episode of multiple sclerosis in 15 per cent of 500 cases of definitely proved multiple sclerosis observed at the Mayo Clinic before 1933. In an additional 40 per cent disturbance of vision occurred sometime during the course of the disease. Usually only one eye is affected at a time. The onset of blindness is rather rapid. It usually proceeds as a gradual blurring or dimness of vision with development of an expanding central scotoma rather than symmetric contraction of the field or the development of sector scotoma. In most instances vision decreases until by the end of the third or fourth day there is no perception of light. After twenty-four to forty-eight hours of blindness, sensation of light reappears and the vision gradually improves, beginning at the periphery of the field. In most instances in which loss of vision is a first episode (or, in cases in which the disease is mild, an early episode), there is a complete recovery of the vision which existed before the attack. In many cases, however, vision is only partially restored, being permanently obscured by a small central scotoma. The onset of blindness in one eye usually is preceded a day or two previously by dizziness, which is sometimes accompanied by vomiting. Some patients attribute their dizziness to a cold and a stuffy sensation in the nose, which in the past has been looked on as reason for suspecting that acute inflammation of the sinuses was responsible for the loss of vision. A second or third attack of blindness, affecting either the same or the other eye or both eyes, may be experienced before any other evidences of multiple sclerosis appear. I believe, however, that a tingling sensation in the extremities and numbness of the feet, legs, arms and hands, with or without repeated attacks of dizziness, vomiting, urinary incontinence and the like, are more likely to occur before a second episode of retrobulbar neuritis occurs.

Most patients suffering from retrobulbar neuritis consult an ophthalmologist a few days after the onset of symptoms. When unilateral blindness occurs without a discernible cause, one suspects interference with the function of vision by a lesion which signifies its situation by the fact that only one eye is involved. The position of the lesion in the optic nerve is further indicated by the appearance of the optic disk.

It has been said that if the lesion lies in the optic nerve anterior to the entrance of the central artery of the retina, the nerve head will show congestion, injection and edema, which are interpreted as "optic neuritis." If the lesion lies posterior to the entrance of the central artery of the retina, the nerve head will show no edema, and the inflammation is said to be "retrobulbar neuritis." During an attack of retrobulbar neuritis, the affected eye is normal in external appearance, and ophthalmoscopic examination reveals no pathologic process in the fundus. After a few days or weeks the nerve head shows a distinct pallor of the temporal portion. If the inflammation has been severe, there is usually marked pallor of the disk and possibly atrophy of a certain portion of the optic nerve, with corresponding diminution in visual acuity and central or paracentral scotoma of size and density corresponding to the intensity of the inflammation.

SCOTOMA

It is presumed that in the first stage of the inflammation the optic nerve is affected by swelling, and the papulomacular bundle, being more vulnerable, more quickly loses its function. Hence the characteristic change in the field of vision consists of central or centrocecal scotoma. Centrocecal scotoma is most frequently associated with diseases of an inflammatory toxic nature that affect the optic nerve. A tumor pressing on an optic nerve at first may produce unilateral central scotoma, but the failure of unilateral vision will be steadily progressive. Lead poisoning and alcohol and tobacco toxemia produce bilateral centrocecal scotoma that appears at about the same time and progresses equally and usually to the same extent in the two eyes. Among patients with multiple sclerosis recovering from acute retrobulbar neuritis, centrocecal scotoma frequently is found, but the lesion usually is present in only one eye at a time. The second eye may become involved within a few days, within a few weeks or not at all. Among 90 cases of multiple sclerosis with retrobulbar neuritis reviewed at the Mayo Clinic, the two eyes were or had been involved in half as many as only one eye, and central scotoma appeared twice as often as centrocecal scotoma. There were as many cases of other types of scotoma as there were of centrocecal scotoma. Central scotoma was present in 50 per cent of the cases, centrocecal scotoma in 25 per cent and other types, including hemianopsia, in 25 per cent. The character of the scotoma indicated, therefore, that the typical toxic inflammatory type of scotoma is found in only 25 per cent of cases of retrobulbar neuritis attributable to multiple sclerosis. Pallor of the disk was present in nearly all patients who had recovered from even mild episodes of retrobulbar neuritis. The degree of pallor varied with the severity of the symptoms. When the condition is mild and transitory there may follow no certain pallor of the disk, whereas marked pallor with atrophy of the nerve head is usually found after a severe attack of blindness or after recurrent attacks. Marked

pallor of the disk without atrophy of the nerve head is not inconsistent with useful vision.

In multiple sclerosis swelling or edema of the disks or optic neuritis is rarely found. In reviewing the literature, Sugar [3] found 36 cases of multiple sclerosis in which definite papillitis or papilledema was described, and he added 2 cases of his own. Of 143 cases in which a definite diagnosis of multiple sclerosis was made, Brown and Putnam [4] reported 4 cases in which papilledema occurred. In a study of 141 cases of multiple sclerosis, Sachs and Friedman [5] found blurring of the disks or mild optic neuritis in 11 and temporal atrophy in 46. (He probably meant "temporal pallor.") In a study of the records of 90 patients suffering from multiple sclerosis with retrobulbar neuritis seen at the Mayo Clinic, some degree of swelling or edema of the disks was found in 8. A comparison of the fields of vision of persons who had swelling or edema of the disks and of those who had no edema or other ophthalmoscopic change at the nerve heads showed them to be entirely similar.

PAIN

Pain as a symptom of retrobulbar neuritis is regarded as of varying significance by different clinicians. In my address to the New York Academy of Medicine in 1933 [2] I stated:

> Pain is not a common symptom in retrobulbar neuritis. Tenderness of the globes, elicited by rotation of the eyes or by digital pressure, is a minor symptom elicited by questioning, but seldom volunteered by the patient.

Further study makes it necessary to alter that statement. In a review of the records of 90 cases in which diagnoses were made of retrobulbar neuritis and multiple sclerosis, it was found that pain was recorded as a symptom in about half. It is possible that in many cases this symptom was not recorded. On the other hand, some patients definitely stated that the onset of blindness was entirely without pain and that there was no physical discomfort. Dizziness and nausea of twenty-four hours' duration preceded the onset of blindness in more than half the cases. Frequently the nausea was attributed to a cold, influenza or indigestion.

Verhoeff [6] stated:

> Pain on pressure and on movement is characteristic of acute retrobulbar neuritis. I use this term whether the lesion is immediately behind the globe or further back; that is to say, whether or not there is edema of the optic disk. I

3. Sugar, S.: Papillitis and Papilledema in Multiple Sclerosis, Am. J. Ophth. **22**:135-139 (Feb.) 1939.

4. Brown, M. R., and Putnam, T. J.: Remissions in Multiple Sclerosis, Arch. Neurol. & Psychiat. **41**:913-920 (May) 1939.

5. Sachs, B., and Friedman, E.: General Symptomatology of Multiple Sclerosis, A. Research Nerv. & Ment. Dis., Proc. (1921) **2**:49-67, 1922.

6. Verhoeff, F. H.: Discussion, Tr. Am. Ophth. Soc. **39**:259-260, 1941.

always regard such cases as cases of multiple sclerosis even if the patient never develops any other symptoms of the disease. I believe that multiple sclerosis can be confined chiefly to the optic nerve.

Few patients complained of photophobia, and only a few wore dark glasses. The mental condition of the patients suffering from complete blindness of one eye often is astonishing. Most of them seem to regard the situation lightly, have no fear of impending total blindness and usually exhibit a state of euphoria. Many patients undergoing their second and third episodes, having recovered from previous attacks of blindness, seem to have no fear. Von Hoesslin [7] pointed out that the prognosis in cases of multiple sclerosis is by no means as hopeless as many textbooks would lead one to believe. Substantial remissions so complete that the patients considered themselves practically well occurred in 17 per cent of his cases.

COMMENT

In many cases retrobulbar neuritis and optic neuritis are attributed to multiple sclerosis by a process of elimination. A careful search must be made for brain tumor and for encephalomyelitis due to toxemia or infection and particularly to toxemia due to an exogenous factor. In 1 instance of retrobulbar neuritis in a child of 5 years, blindness, which became manifest after an attack of measles, was thought to be due to lead poisoning. The child's blindness developed after the fever period and led to complete optic nerve atrophy within a few weeks. At no time had there been other clinical evidence of encephalitis. Abnormal amounts of lead were found in the urine and could be varied by the administration of calcium and by artificially produced fever. The source of lead was traced to the water supply in the child's home. Had she not had fever, it is doubtful whether lead intoxication would have occurred. The presence of lead in a quantity sufficient to produce retrobulbar neuritis is so easily discernible by urinalysis that there should be little confusion between a diagnosis of lead poisoning and multiple sclerosis. The same statement applies to poisoning by arsenic and thallium. It is more difficult to rule out a diagnosis of encephalitis, brain tumor and particularly chiasmal arachnoiditis. In the absence of neurologic findings which would indicate an intracranial neoplasm, a vascular or an inflammatory lesion limited to the optic pathways is most likely. Multiple lesions occurring in the central nervous system at an initial episode may produce simultaneously scotoma and disturbance of function throughout the trunk and extremities associated with signs and symptoms that are so characteristic of multiple sclerosis that the diagnosis is most probable. It has been said, however, that the diagnosis of multiple sclerosis is a "catchall" for cases of retrobulbar neuritis of doubtful etiologic basis.

7. von Hoesslin, R., cited by Putnam, T. J.: The Criteria of Effective Treatment in Multiple Sclerosis, J. A. M. A. **112**:2488-2491 (June 17) 1939.

I cannot refute this statement. On the other hand, I think that a presumptive diagnosis of multiple sclerosis made in many cases in which it may be doubtful that retrobulbar neuritis is present affords the best protection against unnecessary intranasal and intracranial operations. In a review of the cases of retrobulbar neuritis observed at the Mayo Clinic in which multiple sclerosis was suspected at the time of the first examination, some other etiologic factor was not proved in a single case. It cannot be said that the presumptive diagnosis of multiple sclerosis was substantiated in all. Fifty per cent of the patients in this series were examined at the clinic only once. A tentative diagnosis of "retrobulbar neuritis due to multiple sclerosis" was made by the process of elimination, but there was insufficient evidence to make possible a definite diagnosis of "multiple sclerosis." Letters from some of these patients have indicated that other evidences of multiple sclerosis subsequently appeared. The other 50 per cent of patients in this series were seen on two or more occasions over a period of twenty years. Only 1 patient died while at the clinic, and none came to necropsy. From the records, it is rather difficult to be sure of the sequence of episodes in all cases. A statistical compilation of symptoms is impossible because of the paucity of data. However, clinicians' remarks set down on the records at the time of the patients' first visits show that the clinicians favored a diagnosis of multiple sclerosis at that time. In some cases subsequent examinations revealed that the second episode appeared after an interval of more than ten years, but in most cases the interval was much shorter. The patients varied in age from 18 to 64 years, but the greatest number were in the third decade of life. There were 47 men and 44 women.

CONCLUSIONS

The records of more than 400 patients suffering from retrobulbar neuritis, seen at the Mayo Clinic from 1920 to 1940, were reviewed with the intention of determining whether patients for whom a tentative diagnosis of multiple sclerosis had been made experienced further evidence of the disease. The review was made to ascertain whether inclusion of doubtful cases in the category of multiple sclerosis could be justified. By elimination of other factors which might cause blindness, multiple sclerosis was suspected in 90 of the 400 cases. In 41 of these 90 cases further evidences of the disease have appeared. In not a single case in which further symptoms of multiple sclerosis have not yet appeared were the retrobulbar neuritis and the scotoma found to be due to another cause. At the time of the first episode of blindness it was possible in many cases to make a diagnosis of other causes of retrobulbar neuritis, such as arteriosclerosis, diabetes, brain tumor, encephalitis, arachnoiditis and neuritis arising from exogenous toxemia. In some cases of obscure causation a tentative diagnosis was made of one or

another of these probable etiologic factors on the basis of the history or the clinical findings, for example alcohol-tobacco amblyopia, just as in other cases multiple sclerosis was suspected because of the history and of the ocular and general symptoms. It would seem reasonable, therefore, in the absence of signs or symptoms of other causes of retrobulbar neuritis to presume that the condition is due to multiple sclerosis, even though the etiologic basis of the disease cannot be substantiated on any other grounds.

The Mayo Clinic.

DISCUSSION

DR. TRACY J. PUTNAM: Dr. Benedict has given conclusive clinical evidence that the majority of cases of the common form of retrobulbar neuritis should be considered to be instances of the pathologic process seen in multiple sclerosis. I should like to ask Dr. Benedict whether in the cases of quadrantanopsia and hemianopsia the defect was homonymous or occurred in only one eye. If the defect was homonymous, I wonder whether it could have been due to retrobulbar neuritis. Severe destructive lesions may occur in the optic radiations, where they would of course produce such a defect.

From the neurologic point of view, the problem looks very much as Dr. Benedict has presented it. In cases of multiple sclerosis in which a retrobulbar neuritis later develops, tenderness of the orbit and tenderness on moving of the eye are not uncommon. Neither is it uncommon to find symptoms of meningeal irritation in the vicinity of sclerotic plaques occurring elsewhere. With lesions in the brain stem, headache is not uncommon. With myelitic lesions, one may find backache or root pains. One other manifestation which is common to isolated retrobulbar neuritis and to many cases of multiple sclerosis is some change in the spinal fluid—a change in the gold curve or an increase in the protein or in the cells.

Pathologically, also, there is a striking similarity between the two diseases, or rather between the two aspects of what I think unquestionably is the same disease process. As is well known, cases of pure retrobulbar neuritis in which autopsy has been performed are extremely rare. I know of only 2 in the literature, one of Birch-Hirschfeld and the other of Van der Hoeve. In both these cases the lesions described were identical with the lesions seen in acute forms of multiple sclerosis. An ophthalmologist, Roenne, pointed out that the changes in the acute forms of retrobulbar neuritis occurring in almost any demyelinating disease correspond exactly with the changes found in the optic nerves in the majority of cases of multiple sclerosis. A demyelination of the optic nerves, sometimes not accompanied by striking symptoms, is an extremely common observation at autopsy in cases of multiple sclerosis; it occurs in 80 to 90 per cent and in incidence is second only to the demyelination about the ventricles. The changes in the lesions are the same in the two instances: the loss of myelin, which is always prominent, and a lesser, but sometimes striking, loss of axis-cylinders. The latter is a change which has not been emphasized as much as it should be, and yet it is extremely common, especially, doubtless, in those cases in which incomplete recovery occurs. After all, one does see blindness or a

persistent scotoma in many cases of optic neuritis, and one must suppose that in those cases a substantial number of axis-cylinders is destroyed.

I should like to point out one other similarity, and that is the changes in the blood vessels. In the case reported by Birch-Hirschfeld, the retrobulbar neuritis was apparently secondary to a carcinomatous metastasis in the sphenoid cells, which became infected. There was a thrombosed vein which extended into the optic nerve, and the demyelination lay around the thrombosed vein. Recent pathologic investigations have shown that in cases of disseminated encephalomyelitis the demyelination is almost always around thrombosed veins, and the same phenomenon is to be found in miniature in acute plaques of multiple sclerosis. The evidence seems to be accumulating that these two diseases represent simply different stages of fundamentally the same process, which is seen in the acute form in fatal cases of disseminated encephalomyelitis and in the chronic, scarred form in cases of multiple sclerosis. I think this fact is most clearly shown in a curious group of cases of a syndrome known as neuromyelitis optica, which I am sure furnished some of the cases which Dr. Benedict reported. In this syndrome one finds a retrobulbar neuritis, with or without papilledema, and at the same time a transverse myelitis, which may or may not be complete and permanent. Dr. Frank Forster and I looked up a large series of cases of this syndrome and found some 15 unreported ones in our clinics. It seems clear that this disease exists in every degree from an acute necrotic process which leaves behind it blindness or a myelitis which is complete—a complete paraplegia—to a transient retrobulbar neuritis with a transient paraplegia which clears up spontaneously. If the disease is acute and the patient dies of it, one sees the changes in the acute stage; otherwise the patient is apt to recover and then usually has further manifestations elsewhere. This reminds me of a curious bit of circular reasoning which is common at least among my neurologic colleagues. I think that most neurologists would say that multiple sclerosis no longer can be considered an infectious disease. They will say that acute multiple sclerosis exists and is the same as encephalomyelitis. Then, if one asks what encephalomyelitis is, one will usually be told that it is a virus infection. The tendency is to think of retrobulbar neuritis sometimes as an infectious disease and sometimes as a noninfectious disease.

It seems to me that the whole problem becomes clearer if one thinks of both forms of the disease, the acute and the chronic, as not infectious in the sense of a specific infection but as parainfectious, that is, as an abnormal response to any infection and perhaps to some noxae which are noninfectious. This, it seems to me, is the real solution of the old difficulty about the relationship between sinusitis and retrobulbar neuritis. I am convinced that retrobulbar neuritis and attacks of multiple sclerosis can be precipitated by sinus disease, but I believe they can be precipitated just as readily by infection elsewhere in the body. A striking example occurred in a patient of mine who had a first attack of multiple sclerosis following a paronychia of one hand. He recovered from this attack and a year later had a similar attack following another paronychia. He recovered from this attack also, with a little retrobulbar neuritis remaining; but since that time, whenever he has sinusitis, which is every two or three years, the same condition flares up again, he has many of his former symptoms and he is left a little worse off than he was

before the sinusitis. In the group of cases which Dr. Brown and I observed at the Boston City Hospital, almost the only therapeutic measure which seemed to have any reasonable success was the looking for and cleaning up of foci of infection, usually in the tonsils or the teeth. I feel that the search should not be confined to the sinuses. A relationship to nonspecific infections is clearly shown by some cases of disseminated encephalomyelitis, which is the commonest type of encephalitis now seen. Statistics show that, contrary to what one was taught to believe, the cases following measles and vaccinia are in a minority. Most cases follow focal infection around the nose or throat or bronchopneumonia; next in frequency are the cases in which there is no obvious infection elsewhere in the body, and of least frequency are those which follow the so-called specific infections, such as measles, vaccinia and a reaction to inoculation against rabies.

If a means of halting the progress of multiple sclerosis is ever found, ophthalmologists must be ready to apply it in cases of retrobulbar neuritis.

DR. JAMES W. SMITH: In 1933, when Dr. Benedict presented his paper before this section, I referred to a young man with retrobulbar neuritis who was seen by a rhinologist. Sufficient paranasal disease was found to warrant surgical intervention. The surgeon presented the case during a remission phase as one of retrobulbar neuritis cured by operation. Optic nerve atrophy and definite multiple sclerosis later developed. I am glad that Dr. Benedict has stressed the relative unimportance of sinus disease in the type of retrobulbar neuritis under discussion.

I should like to know if the vasodilators were found to be of benefit in his present series of cases.

DR. W. GUERNSEY FREY JR.: Dr. Benedict mentioned that the diagnosis of multiple sclerosis had saved a large number of patients with retrobulbar neuritis "from unnecessary intracranial and intranasal operations." Does he imply that those patients with retrobulbar neuritis who recover after sinus operations have been operated on unnecessarily? Of his series of 400 cases of retrobulbar neuritis, a diagnosis of multiple sclerosis was made in 91; in 40 odd of these the diagnosis of multiple sclerosis was subsequently confirmed, and in the remaining cases it was not disproved. Would Dr. Benedict give a brief summary of the etiologic diagnoses in the other 309 cases of his series?

DR. CONRAD BERENS: Dr. Benedict's contribution is much appreciated, and there are several questions I should like to ask. One is, Was pain complained of by the patients? Was it seasonal? Did it have any relation to the type of pain associated with sinus disease? The second question concerns basal arachnoiditis. Can Dr. Benedict tell anything about the differential diagnosis as it pertains to this disease? The third question concerns sinus disease. It certainly seems evident that there must be more sinus disease in the East than in the Middle West, and I believe that in some cases of retrobulbar neuritis in the East the condition is caused by sinus disease. One certainly sees patients who are benefited by treatment of the sinuses, and the retrobulbar neuritis does not always recur after sinus operation. Sinus operation, however, does not cure chronic sinus disease, and surgical intervention should be postponed until medical treatment has been given a thorough

trial. The question is, What sort of diagnostic technic does Dr. Benedict employ in his cases of chronic sinus disease? There are excellent men at the Mayo Clinic. Do they use laminography?

Do I understand correctly that 91 patients showed no evidence of posterior sinusitis, that is, infection in the posterior ethmoid cells or in the sphenoid cells? Here, in this locality, I would think that if one took roentgenograms of 91 patients who had multiple sclerosis one would find a large percentage with evidence of sinusitis.

Another question is, Did Dr. Benedict have cultures made in these cases? A large percentage of my patients with chronic recurring ocular lesions, some with retrobulbar nerve involvement, had toxic coliform bacteria in their sinuses. I tried to obtain the opinions of other persons in regard to coliform bacteria in the sinuses. Communications from specialists on the nose and throat in various parts of the country revealed little information. It is known, however, that these bacteria are highly toxic and that they do occur in some patients with retrobulbar neuritis. The fact that some of the patients apparently improved with treatment of coliform bacteria and other infections of the upper respiratory tract is the reason why I am inquiring about the cultural work. Dr. Putnam said that in some cases the disease is on an infectious basis, and one of the best methods of curing it in these cases is to find the infection and treat it. I have had no success in finding a virus even when the patient seemed to have had his difficulties after an attack of influenza.

DR. WILLIAM L. BENEDICT: I am grateful to Dr. Putnam for his discussion. My main objective was to justify placing in the category of patients with multiple sclerosis patients having retrobulbar neuritis when a better reason cannot be found for placing them in some other category. I cannot discuss all the questions that have been asked, but I shall refer briefly to some of them.

First, in regard to Dr. Putnam's question as to the character of the quadrantanopsia: There were in this series a number of persons suffering from multiple sclerosis with bilateral or homonymous scotomas and hemianopsia. Since my paper was written, I have seen an additional patient with homonymous quadrantanopsia of the left lower quadrants and early multiple sclerosis. Although the visual fields had partly returned, there was a persistent scotoma in the lower left quadrant in each field.

Examination of the spinal fluid was made in all the cases. In some cases there was no abnormal change in the gold curve. The neurologic consultants in some instances strongly suspected multiple sclerosis and made that diagnosis on the basis of general symptoms and neurologic signs in spite of negative spinal fluid findings. I recognize that changes in the spinal fluid characteristic of multiple sclerosis may also be found in other demyelinating diseases and in some infectious diseases.

I did not include patients with neuromyelitis optica in this group. The number I have seen and recognized is small, and the patients have all been children.

I hoped that some one would ask this question: "Did any of the patients whom you did not put in this group with multiple sclerosis, but in some other group, with a diagnosis such as brain tumor or arterio-

sclerosis, have symptoms of multiple sclerosis later?" I think that some were missed. The reason I say that is because in a previous survey, of 500 patients with definitely proved multiple sclerosis, 125 had had optic neuritis or retrobulbar neuritis, while of this series of 400 patients with retrobulbar neuritis, 91 were suspected of having or proved to have multiple sclerosis. I do not mean to say that every one was properly classified at the first examination, but among those who were put in the group with multiple sclerosis, in none was blindness proved to be due to any other disease.

Dr. Berens has brought up the question of basal arachnoiditis. In the ophthalmologic department of the Mayo Clinic a diagnosis of arachnoiditis has been made in a number of cases on the basis of the history and the character of the visual disturbance, and the diagnosis has been verified at operation in every case. It is not difficult to distinguish multiple sclerosis from arachnoiditis.

I think I do not have time to go into a discussion of sinus disease. In this series there were no patients with retrobulbar neuritis due to acute sinus disease of sufficient intensity to warrant surgical intervention. Chronic sinus disease, which Dr. Berens seems to think is so prevalent in the East, is probably prevalent everywhere in the world, but I believe it does not result in demyelination except in cases of direct invasion. And I think there is not sufficient reason to believe that coliform bacilli or other common types of organisms give rise to multiple demyelination of the type seen in multiple sclerosis. Pain was a recorded symptom in about 50 per cent of the cases. Dr. Putnam used the term "parainfection." It may be useful in expressing what I think about multiple sclerosis in relation to infection.

SIMPLE QUANTITATIVE TEST FOR ACUITY AND RELIABILITY OF BINOCULAR STEREOPSIS

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Previously I have described three tests [1] for binocular stereopsis, each of which utilizes one or more new principles. These tests are essentially only qualitative, although the kinetic test, the most useful of the three, does permit acuity to be estimated with considerable accuracy. About five years ago I devised a test based on an entirely different principle, that of presenting misleading monocular criteria so as to make binocular parallax the only correct evidence of relative depth and to cause perception of false depth when this correct evidence was not perceived. So far as I am aware this principle had never before been purposely employed. During the past year I have made the test accurately quantitative. One of its important advantages is that it reduces to a negligible factor the possibility of correct guessing. The test is simple and is made without the use of a stereoscope, amblyoscope or, in fact, any viewing instrument. Such instruments often seriously interfere with stereoscopic perception and for this and other reasons do not permit accurate determination of its acuity.

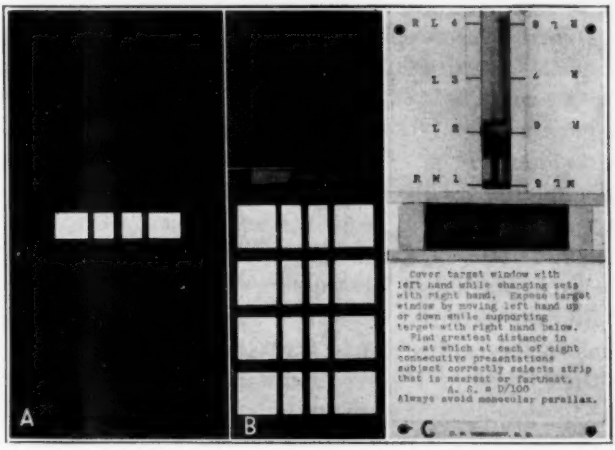
The misleading monocular criteria I now employ consist only of size differences. The additional introduction of intensity differences I have found unnecessary. Moreover, it makes the test more difficult to standardize. Objection may be raised to the misleading size differences on the ground that they may prevent the acceptance of the evidence provided by binocular parallax. But except under certain artificial conditions, this evidence of relative depth is always correct, and it therefore should always be relied on in preference to evidence that is often incorrect. If not thus relied on it would be of little value, since objects in the visual field are almost always unequal in size and their relative sizes often incorrectly indicative of their relative depths.

Only a simple single device is required for the test. To face the observer is a rectangular black screen (target screen) at least 9 by 17.5

Read before the Section of Ophthalmology of the American Medical Association at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Verhoeff, F. H.: (*a*) A Simple Test for Stereoscopic Vision, Ophth. Rec. **12**:205, 1903; (*b*) An Improved and a New Test for Stereoscopic Vision, Am. J. Ophth. **16**:589, 1933; (*c*) A Kinetic Test for Stereoscopic Vision, Arch. Ophth. **15**:833 (May) 1936.

cm. in size, with its long axis vertical (view *A* of the accompanying illustration). In this is centered a rectangular window (target window) 1 by 5.4 cm. in size, with its long axis horizontal. The edges of the window are sharp. The side edges are beveled toward the front and the upper and the lower edges toward the back of the device. Immediately behind this window, held so that it can slide only vertically, is a smaller screen (sliding screen) 11 cm. high, 6.9 cm. wide and exactly 2.5 mm. thick (view *B*). The sliding screen contains four rectangular windows, each 16 by 50 mm. in size. These are centered on the vertical midline with their long axes horizontal and are separated from each other by distances of 5 mm. Crossing each window vertically are three thin black strips, 3 mm., 2.5 mm. and 2 mm. in width, respectively. Of


A
B
C
Cover target window with left hand while changing sets with right hand. Expose target window by moving left hand up or down while supporting target with right hand below.
Find greatest distance in cm. at which at each of eight consecutive presentations subject correctly selects strip that is nearest or farthest.
A. C. e D/100
Always avoid monocular parallax.

Components of the device used (one-third actual size). *A*, the face of the device, showing the target window with a set of strips exposed. *B*, the sliding screen, showing the four sets of strips. *C*, the device as seen from behind, showing the translucent screen and the markings for sets of strips.

the strips, some are affixed to the back and the others to the front of the sliding screen. There is, therefore, a depth of 2.5 mm. between the strips at the front and those at the back. By moving the sliding screen, one can expose any of the four sets of strips in the target window, and by turning the device upside down, one can reverse the positions of the lateral strips. The sets are numbered from below upward. In each set the 3 mm. strip is centered exactly on the midline, while at one side the 2.5 mm. strip is centered 10.75 mm. and at the other side the 2 mm. strip is centered 10.50 mm. from the midline. In set 1, the middle strip is at the front, the 2.5 mm. strip at the back on the left and the 2 mm. strip at the front on the right. In set 2, the middle strip is at

the back, the 2.5 mm. strip at the back on the right and the 2 mm. strip at the front on the left. In set 3, the middle strip is at the back, the 2.5 mm. strip at the front on the left and the 2 mm. strip at the back on the right. In set 4, the middle strip is at the back, the 2.5 mm. strip at the front on the right and the 2 mm. strip at the front on the left.

Behind the target window and about 3 mm. behind the sliding screen is a translucent diffusing screen of ample size (5.8 by 2 cm.). This is indirectly attached to the target screen and is therefore stationary. The diffusing screen is evenly illuminated from behind. The character and the intensity of the light are unimportant within wide limits, even more so than for tests of the visual acuity. Ordinary daylight from a window is satisfactory. Over the back of the device (view *C*) is a protective cover suitably marked so that any one of the sets of strips can easily be identified from behind and, by the aid of a knob, placed in position by the examiner. On the face of the device there should be no telltale defects by which an astute observer might detect whether or not it had been turned upside down. The strips should be as lusterless as possible, and no perceptible light should be reflected on their faces from within the target window.

I have employed for the target screen one layer and for the sliding screen two layers of cardboard 1.25 mm. thick. The desired depth of 2.50 mm. was thus obtained. For the strips I have used thin black paper. To avoid warping I have used as an adhesive "grippit" instead of glue. For the diffusing screen I have used translucent celluloid film.[2] Constructed in this simple way, the device has been sufficiently durable for my purposes. For commercial manufacture the construction should be more substantial. The strips should consist of triangular prisms with their apexes pointing backward. A removable attachment for artificial illumination should be provided. I have found that a 2.2 volt flashlight bulb and a curved reflector made of white paper furnish artificial illumination that is uniform and more than adequate.

During a test the device should be kept centered as a frontal plane on the subject's binocular visual midline. To avoid monocular parallax it is highly important to hold the device steady and particularly not to rotate it on its vertical axis. It is, of course, also important not to permit the subject to move his head.[3] The target window should not be exposed while the device is being placed in position or the sets are changed. A convenient method of manipulation is to grasp the device over the target window with the left hand, place the desired set into position with the right hand and then grasp the device below with the

2. Frosted transparent nitrate cellulose, obtainable from Landers Brothers Co., Boston.

3. The use of a pseudoscope would make these precautions unnecessary but would introduce serious disadvantages.

right hand and expose the target window by moving the left hand up or down. Thus, while the target window is exposed the device is supported by both hands of the examiner.

The correctness of a selection depends solely on whether the strip that is alone the nearest or the farthest is correctly selected. However, a request to make the selection might confuse the subject. A satisfactory request, easily understood, is, "Select the nearest strip and the farthest strip, unless they all appear to be at the same distance." Of course, in response to this request, the subject may state that two or all three of the strips appear at the same distance if they so appear to him. As a matter of fact, two strips in each set are equally distant. Selection of one of these as the nearer of the two should not be regarded as incorrect. The larger is almost always selected as the nearer. A request should never be so worded as to assist the subject in making a correct selection, and he should not be given information as to the correctness of his selection. This information might affect his subsequent judgment. Needless to say, errors of refraction, including presbyopia, should be corrected unless it is desired to ascertain their effect.

The test is made as follows: The device with set 2 presented is placed at a distance of about 40 cm. from the subject and then brought nearer if necessary. This preliminary procedure is to acquaint him with what he is to observe and at the same time determine whether there is at least a short distance at which he can select the correct strip in this set. If he is unable to do this even at his near point of convergence, either he may entirely lack binocular stereopsis or its acuity may be too low to be determined by the depth difference in the device. If at some near distance the subject's selection is correct, the device is placed at a distance of about 2 meters and brought nearer with a different set exposed. Whenever the subject's selection is correct the set is changed, and whenever his selection is incorrect the distance is decreased by a step that accords with the Snellen notation. In this way the greatest distance, D, in centimeters, is soon found at which his selection is correct for all of eight different but consecutive presentations. Four of these, of course, are obtained by turning the device upside down. By this test the subject's acuity of binocular stereopsis, *AS,* is $\frac{D}{100}$. This fraction I convert into the Snellen notation. Thus, if D equals 100, AS equals 20/20, or if D equals 50, AS equals 20/40.

For the preliminary procedure sufficient time should always be allowed to insure that the subject fully understands what he is to observe. After this the time factor depends chiefly on his quickness of speech. For usually if he can make a selection, he can do so in less than a second. The time required for the test is short because it is necessary to change the sets only a few times before the entire eight presentations are made. The distance D can usually be estimated with sufficient

accuracy by the examiner without being measured. However, a long rod marked according to the Snellen notation is convenient for measuring it. The rod is held in proper position by the subject, one end of it pressing against his chest.

If, as in the case of an aviation candidate, it is desired to ascertain only whether the subject's acuity meets a certain requirement, the test becomes still simpler. Then, after the preliminary procedure is carried out, all that need be done is to make the presentations at the required distance.

Since, owing to difficulty in convergence, 10 cm. is about the shortest distance ever employed in binocular vision, the lowest acuity ordinarily determinable by the test is 20/200. By providing sets with greater depth, still lower grades could be determined. It is doubtful, however, that this would be worth while. For an acuity lower than 20/200 would be of little value. It would not, under similar conditions, enable the subject to perceive depth differences of 2 cm. at a distance of 30 cm., of 25 cm. at 1 meter or of 90 meters when the nearest object was at a distance of 6 meters. The demonstration of acuities lower than this might be of considerable scientific interest, especially in certain cases of strabismus, but it would be of no direct practical importance. I have elsewhere touched on this question.[4] When the acuity of binocular stereopsis is below 20/200, all that need be ascertained is whether binocular stereopsis exists at all. For this purpose my kinetic test [1c] is especially useful, although it requires the use of a stereoscopic viewing instrument.

The dimensions of the device and of its parts are unimportant within rather wide limits, but it is highly important for them to be precisely standardized, especially if the test is to come into general use. They were based on theoretic considerations, convenience and, finally, on actual trials. The height of the target window approximately accords with that best suited for the perception of binocular parallax under the conditions of the test. The width and the position of the window make binocular parallax produced by the strips and the sides of the window less perceptible than that produced by a forward and a rear strip. The sharpness and the backward beveling of the upper and the lower edges of the window prevent the strips from casting perceptible shadows on these edges and thus revealing the relative depths of the strips. The sizes and the differences in size of the strips were made only sufficiently great to be always easily perceptible by any one whose visual acuity is adequate for the test. I feared that the depths to which greater size differences would correspond might be entirely rejected

4. Verhoeff, F. H.: Anomalous Projection and Other Visual Phenomena Associated with Strabismus, Arch. Ophth. **19**:663 (May) 1938.

as unreasonable under the existing conditions. The chief purpose of the wide spacing of the strips was to make the perceptibility of the depth difference decrease to a considerable extent as the distance of the device from the subject decreased. Another purpose will be explained in connection with the question of cheaters.

The selection of the unit distance, 1 meter, was based partly on convenience but chiefly on the fact that as distance from the observer decreases, the more greatly binocular parallax exceeds in importance difference in size. The fixed depth difference of 2.5 mm. was selected because with this I pass the test at 2 meters, and my visual acuity in each eye (20/10-Snellen) and my acuity of stereopsis are unusually high. Therefore, with the device as now constructed, normal acuity of binocular stereopsis equals 100/100 equals 20/20. For this acuity and an interocular distance of 62 mm., the binocular parallax is 32 seconds. For 20/15 it is 18 seconds and for 20/10 8 seconds.

The system I have adopted for grading the acuity of stereopsis has never previously been employed for this purpose, although it is analogous to the Snellen system for grading the acuity of vision. In the Snellen test, an acuity of 20/40 is less than one-half an acuity of 20/20 on the basis of minimum separable. For in this test are concerned other important factors, and these as well as minimum separable itself must vary to an important extent with length of contour—facts commonly overlooked. Similarly, in my test the notation does not exactly accord with geometric progression based on minimum perceptible binocular parallax. However, because for a fixed depth difference, binocular parallax varies inversely nearly as the square of the distance, it must not be assumed that, for instance, an acuity of binocular stereopsis of 20/40 is only one-fourth an acuity of 20/20. For the perceptibility of the parallax considerably decreases with an increase in size of the visual angles of the widths of the strips and of the intervening spaces, and these angles vary inversely as the distance. The fact of practical importance in this connection is that if according to the test one person has an acuity higher than that of another, the difference between their acuities is somewhat greater than that indicated by the notation employed. This fact emphasizes the importance of standardizing the device.

While my test does not directly determine the least binocular parallax perceptible near the fixation point, this probably could be closely correlated with and then computed from the results obtained. An acuity of 20/10 by my test, although based on a binocular parallax as great as 8 seconds, might well mean that under certain other conditions the subject could often perceive a parallax of 1 second. The chief purpose of the test, however, is to provide a simple method by which acuities of stereopsis can be rapidly graded and compared, as are visual acuities

by means of the Snellen test. My reason for utilizing the Snellen system of grading and of notation is that for visual acuity the practical value of each has been established by years of wide usage.

Tests that I have thus far made on various persons indicate that an acuity of binocular stereopsis of 20/20 by my test can be regarded as normal in about the same sense that a visual acuity of 20/20 by the Snellen test can be so regarded. By my test, as by the Snellen test, many persons have an acuity much higher than "normal." In the two tests, what is meant by "normal" is equally unimportant. With my test, data could be accumulated for ascertaining the correlation of acuity of stereopsis with acuity of vision and with degree of efficiency in various occupations and sports. Such data would also provide a basis for agreement as to what should be regarded as a normal acuity of stereopsis.

For the sets of strips there are possible in respect to the fixed depth three other arrangements in addition to the four that I have utilized. These are: all strips even, the largest in front alone and the smallest behind alone. I have omitted these for the reason that a subject with inadequate stereopsis could correctly make the required selection from each by the aid of the size differences. In other words, I have omitted three sets of strips because the size differences in them would not be sufficiently misleading. These sets would be useful only in the examination of cheaters, and such subjects are otherwise sufficiently handicapped in the test.

There are two purposes for the provision of turning the device upside down. One is to provide eight different arrangements, two in respect to right and left for each of the four in respect to depth. The other purpose is to allow for the difference in depth perception which sometimes exists for objects on the right and on the left.

On the basis of whether or not he has familiarized himself with the test, a subject may be classified as practiced or unpracticed. At each presentation the practiced subject would by guessing make his selection from four different arrangements in respect to depth, and the unpracticed subject, from seven. Hence, by disregarding the size differences and merely guessing, there is for the practiced subject with inadequate stereopsis only one chance in 65,536, and for the unpracticed only one chance in 5,764,801, of not making at least one mistake in the eight presentations.

In the case of a practiced subject it is especially important that he should always be requested to select the nearest and also the farthest strip. For a request to select, for instance, only the nearest strip would be an important clue for him. It would mean that one strip was the nearest and therefore the two others were the farthest. In the case of a practiced cheater, the device should be hidden from view when

it is turned upside down or the sets are changed. Moreover, the sets should be changed at random instead of in the sequence noted on the device. A set of eight small slips of paper, or balls, consecutively numbered and drawn at random from a receptacle provide a convenient means of deciding the sequence in such cases.

If in the device the strips were of equal size, the test, owing largely to the procedure employed, would still have important advantages. There are two great advantages gained by making the strips of unequal size. One is that the size differences render it always impossible to make a correct selection by means of difference in image size. The other is that when the binocular parallax is not perceptible, the subject is induced not only not to guess but to make an incorrect selection. There is, of course, for every subject with binocular stereopsis a range of distance within which he perceives the binocular parallax only at times and beyond which he never perceives it. This may be termed the range of uncertainty.

When the strips are made of equal size in the device and the distance is not too great, the subject can determine the existence of the fixed difference in depth by difference in image size. When the distance is too great for a subject with inadequate stereopsis to do this, he is compelled to guess in order to make a selection. But even more serious is the fact that I have found without special effort subjects who could with one eye occluded select the forward strip in at least eight consecutive presentations at 1 meter. They said the strip appeared forward but were unable to explain why. Hence the evidence, whatever it was, must have been subconsciously perceived. Possibly it consisted in difference in image size and the difference in intensity associated with this. It is true that these differences were slight, but some subjects might subconsciously detect them. In addition there may have been some other seemingly trivial but subconsciously perceptible peculiarities associated with the forward position of the strips.

All these difficulties are eliminated by making the strips of unequal size. Then, since difference in focus is always far too slight to be recognizable, binocular parallax is the only correct evidence of relative depth, and opposed to this evidence there is always the incorrect but easily perceptible evidence supplied by the size differences. With the device thus constructed, I have never found a subject who was completely lacking in binocular stereopsis to select the correct strip. I have tested many squinters binocularly and many persons, including myself, monocularly. Some of these subjects stated that all three strips appeared at the same distance close behind the target window. This was no doubt because the diffusing screen appeared to them to be there. The majority, nevertheless, stated that the largest strip appeared to be the nearest. None selected the correct strip.

The question answered by the test when it determines the distance, D, is, What is the maximum acuity of binocular stereopsis on which the subject can rely? The importance of this question is obvious from the fact that the reliability of action, either voluntary or involuntary, depends not only on the acuity but on the reliability of the perception that controls it. The answer is satisfactory for the following reasons: 1. As already pointed out, the possibility is negligible that the subject merely by guessing could make eight consecutive correct selections. Hence, he must, at least at times, possess the ability to perceive at D the depth difference by means of binocular parallax. 2. His only correct evidence as to the depth difference at each presentation is binocular parallax, and this evidence is opposed by the size differences. Hence the assumption is satisfactory that the subject if honest has for each selection at D utilized his ability to perceive the depth difference. 3. This assumption is confirmed and the reliability of the acuity D/100 established by the fact that he has made eight consecutive correct selections at D. 4. Since D is the greatest distance at which the subject has made eight consecutive correct selections, D/100 is the maximum acuity on which he can rely. In no test, especially a subjective one, are the conditions exactly repeatable. Hence it is not to be expected that exactly the same result will be obtained if the procedure is repeated. The same kind of difficulty exists in the Snellen test for visual acuity. Of course, just as in the case of the Snellen test, if the subject is unreliable, his maximum reliable acuity may be higher than that revealed by the test.

It is to be noted that whether the question discussed is satisfactorily answered depends on whether the requirements as to number of presentations and number of correct selections are satisfactory. If they are not regarded as satisfactory, they can be made so to any reasonable extent by suitably changing the numbers.

Some subjects, especially if they were aviation candidates eager to be accepted, might attempt to pass the test dishonestly. A practiced cheater might attempt to identify the different sets by comparing the apparent sizes and spacing of the strips. He would be unsuccessful for the following reasons: 1. The strips in each set are so different in size and so far apart that their apparent sizes cannot be accurately compared. 2. The sets are not simultaneously presented, and hence the apparent sizes of the strips in different sets cannot be directly compared. 3. The differences in image size produced by the depth difference are far too slight to be recognizable—that between a rear and a forward 3 mm. strip corresponds to only 0.075 mm. at 10 cm. and to only 0.0075 mm. at 1 meter. 4. Apparent differences in spacing are not definitely specific and even by a cheater could not possibly be recognized beyond a distance of 50 cm.

An extraordinarily astute cheater might attempt to make his unreliable acuity appear to be reliable by guessing only at those presentations at which his perception did not accord with any of the four possible correct selections. He would need to guess correctly each time, and his chance of doing this would be slight. Moreover, he would be likely to make at least one disqualifying mistake when he relied on his perception. In general it is safe to say that a cheater, no matter how astute he may be, has no greater chance of passing the test at the critical distance than has an honest subject with the same acuity.

The foregoing brief discussion has not distinguished between conscious and subconscious perception of relative depth. I have previously pointed out [5] and later emphasized [4] the fact that the conversion of binocular parallax into depth meaning takes place only below the level of consciousness, that is to say, only in a subconscious mechanism. That this is true should long ago have been evident from the well known facts that so-called physiologic diplopia is seldom perceived and when perceived is not consciously interpreted as depth. Many persons with excellent stereopsis have never perceived it. It is almost never perceived when the binocular parallax which could cause it is relatively slight and therefore of the greatest importance.

The test obviously proves the subconscious mechanism to be reliable when it proves that the conscious perception which depends on it is reliable. Obviously, also, it proves that the subconscious mechanism is more reliable than the conscious perception if the subject does not feel sure at each of his correct selections at D or at a distance less than D. In such a case the subject could not be relied on to perform any voluntary act which depended chiefly on his highest acuity of stereopsis.

The procedures thus far described do not, of course, determine the ability of a subject consciously to estimate the amount of depth difference he perceives by means of binocular stereopsis. This ability is acquired by experience and therefore depends on the subject's ability to learn by experience. For obvious reasons, such estimation is usually most accurate in the case of objects within easy reach of the hands. At such a distance the subject's ability to estimate amount of depth difference by binocular parallax alone may be determined by a simple additional procedure. It is only necessary to place the device at a distance of about 30 cm. and request the subject to estimate the depth between the strips in units of measure with which he is familiar. A convenient unit at once available to him is the width of the 2.5 mm. strip, a width exactly equal to the distance to be estimated. Or he could be requested to select the strip whose width most closely corresponded to the depth difference.

5. Verhoeff, F. H.: A New Theory of Binocular Vision, Arch. Ophth. **13**: 151 (Feb.) 1935.

In the case of a cheater, provision for changing the amount of depth difference in one of the sets of strips would be necessary. Probably as a routine test such a determination would not prove to be of practical value. For most persons, no doubt, estimate difference in depth subconsciously more accurately than they can consciously, since their experience in this estimation is chiefly subconscious. In the case of an aviation candidate, a requirement that he pass such a test without practice would be unfair, since presumably he would lack the necessary conscious experience. However, inability to pass the test after practice would be strong evidence that for purposes of flying he would be unable to learn to utilize adequately his acuity of stereopsis. In fact, it would be strong evidence against his ability to learn to perform satisfactorily any act requiring delicate conscious judgment.

In the usual test, an incorrect selection does not always completely accord with the size differences. For example, when the 2 mm. strip is actually the nearest and the 3 mm. strip is selected as the nearest, the 2.5 mm. strip may be selected as the farthest. No doubt such a selection means that the device is in the range of uncertainty and that a compromise has been made between the binocular and the monocular evidence. After a subject has discovered by means of binocular parallax that a lateral strip is the nearest, this strip may for a brief time continue to appear nearest when one of his eyes is occluded. He is relying not on the immediate "evidence of his senses" but on the previous binocular evidence. Similarly, if the test is first made with one of the eyes covered, an occasional subject, even if he has high acuity of stereopsis, may not at once accept the binocular evidence presented when his eye is uncovered. Occasionally, a subject with binocular stereopsis will state that both lateral strips appear nearer than the middle strip just before he correctly perceives that only one is nearer. From a psychologic standpoint these are interesting but perhaps not surprising facts. They do not affect the reliability of the usual procedure.

Other interesting facts could be ascertained by means of the device, some of which might prove to be of practical value. The minimum exposures required for certainty of perception of the same depth difference at various distances could be determined. Also could be determined the delays in stereoscopic perception occasioned by various changes in fixation and convergence. Effects of aniseikonia on stereoscopic perception could be investigated by this device and slight modifications of it, provided that the aniseikonia itself had been demonstrated with sufficient accuracy.

The device can also be used to ascertain whether a subject possesses the ability to perceive relative depth by means of monocular parallax. The simplest way to do this is suitably to rotate the device on its vertical axis after occluding one eye of the subject. I have not yet made a statistical

study of this ability, but I have found that it is possessed in high degree by many subjects with binocular stereopsis. I have also found that while many subjects who have always lacked binocular stereopsis perceive at once the meaning of monocular parallax, many others, surprisingly enough, never perceive it. These results were also obtained when the monocular parallax was elicited in other ways.

I shall now compare my test with the Howard-Dolman, for the latter and similar tests are the only ones now commonly employed for measuring acuity of stereopsis.[6] The two tests differ almost diametrically in many respects. One of their differences is unimportant—a change in binocular parallax is produced in the Howard-Dolman test by changing the depth and in my test by changing the distance of the device from the subject. Each method is the more practical for the test in which it is used. Other differences between the tests are highly important..

Thus an attempt is made in the Howard-Dolman test to determine the average maximum depth difference that is not perceived in a few trials, usually only three, made under identical conditions and in my test to determine the minimum depth difference that is perceived in each of eight observations under different conditions. In the Howard-Dolman test, the objects are two in number and equal in size; in my test, they are three in number and unequal in size. The Howard-Dolman test is made at a far distance, 6 meters, and my test at a near distance, less than 2 meters. In the former the target window is so narrow that binocular parallax produced by the test objects and the edges of the window is a possible cause of serious error. In my test this possibility of error is eliminated by the width and the position of the target window. In the Howard-Dolman test guessing is always possible as an important factor; in my test it is always reduced to a negligible factor.

From what I have already said it is perhaps sufficiently obvious that for the determination of acuity of binocular stereopsis my test is greatly superior to the Howard-Dolman test. However, in this connection it may be well to emphasize certain facts that are commonly overlooked. One of these is that when two objects are of the same size and the subject assumes this to be the case, he can, by comparing their retinal images, determine when the objects are at the same distance much more accurately than he could if they were of unequal size, even if he knew their exact difference in relative size. This fact is six times more serious for the Howard-Dolman test than it would be if the test were made at 1 meter, for then the ratio of difference in image size to image size would be one-sixth as great for the same binocular parallax.

Another of the facts is that when the two objects are of equal size a subject can subconsciously observe the rate of change in difference in

6. Armstrong, H. G.: Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939, p. 77.

image size and thus guess when no difference exists. Still another fact commonly overlooked is that a subject can similarly guess the rate of change in binocular parallax and thus guess the time when no binocular parallax exists. In addition to either or both of these ways of guessing, he can employ the method of splitting the difference. He can guess more accurately when, as is usually the case, he is permitted to move the test object, but he can do so with considerable accuracy when the test object is moved by the examiner. Every subject who passes the Howard-Dolman test probably subconsciously employs one or more of these methods of guessing, whether or not he has adequate stereopsis. In such ways substandard acuity can be made to appear standard or even above standard. Certainly the Howard-Dolman test never excludes this probability.

Another fact commonly overlooked is that determination of the least relative depth perceptible at a given distance is of more importance than determination of the greatest relative depth imperceptible at this distance. For recognition of relative depth is ordinarily of more importance than recognition of its lack. Obviously this is true in the case of an aviator attempting to land his plane. Moreover, more reliance is placed on depth evidence provided by binocular parallax than on lack of such evidence—binocular parallax will not only overcome but often completely reverse strong evidence to the contrary, whereas lack of it will not overcome even slight evidence to the contrary. These facts are utilized in my test but entirely neglected in the Howard-Dolman test. They are demonstrated to be true when, for example, set 1 of my device is viewed binocularly by a subject with adequate stereopsis. Then on account of binocular parallax the strip on the right appears nearer than that on the left in spite of difference in size which indicates the reverse, whereas it usually appears farther away than the middle strip on account of difference in size and in spite of lack of binocular parallax. Elsewhere [1b] I have demonstrated these facts even more convincingly. Probably so little reliance is placed on lack of binocular parallax because of the facts that in monocular vision this lack always exists and must be ignored and that even in binocular vision this is the case for distant objects and when pictures are viewed.

What I have just pointed out explains why in my test the subject can feel perfectly sure by means of sufficient binocular parallax that one strip is nearer than another even though their relative sizes indicate the reverse and why in the Howard-Dolman test the subject can never feel sure by means of lack of binocular parallax that the rods are at the same distance even when they actually are and even though they are of the same size.

In the Howard-Dolman test the minimum requirement means that a depth difference of 30 mm. must not be perceived. For an interocular

distance of 62 mm. this corresponds to a binocular parallax of 11 seconds. For the reasons given, this does not mean that any greater parallax can be perceived. In other words, it does not necessarily mean that binocular parallax can be perceived at all. While the parallax of 32 seconds required for an acuity of stereopsis of 20/20 by my test may seem high, it must be remembered that this acuity means not only that the subject can perceive this parallax but that he can rely on doing so. An acuity of 20/10 by my test means that the subject can rely on perceiving a parallax of 8 seconds. Just what acuity by my test should be required of an aviation candidate remains to be definitely determined, but it would seem that it should not be less than 20/20 so long as a sufficient number of candidates could meet this requirement.

Although the Howard-Dolman test cannot be relied on for determination of the acuity of binocular stereopsis, it might be of some value if my test was also used. If the subject passed my test it would mean that he possessed adequate acuity of stereopsis. If he then failed to pass the Howard-Dolman test it would mean that his experience had not taught him to utilize this acuity for certain purposes that might be of value to an aviator. If later, after brief practice with the Howard-Dolman procedure, he could pass the test, it would almost certainly mean that as concerned stereopsis his learning ability was high.

The basic principles of the test originally employed by Howard [7] were sounder than those of the test now known as the Howard-Dolman test, which I have just discussed. Howard attempted to determine the least relative depth perceptible at a fixed distance and also attempted to allow for guessing. His method required the subject to make from twenty to one hundred observations and was abandoned probably because it was, therefore, too time consuming. Owing to the same cause, another objectionable feature was that it introduced fatigue as an important factor. Since Howard's original method has been generally abandoned, I need not discuss it at length. However, it may be well to point out that it would be greatly inferior to my test if only because it had the objectionable features mentioned and still more so if only because the test objects were equal in size.

In ordinary office practice I have found my device eminently satisfactory when constructed and used as described. A more elaborate apparatus is preferable for the testing of numerous aviation candidates, for use in a large clinic and for scientific research. For such purposes a substantial support along which the device can be moved, standardized artificial illumination and an adjustable head rest are advantageous. It is also advantageous to replace the sliding screen by a wheel with eight windows, so that any one of the eight different presentations can be made without turning the device upside down. This requires

7. Howard, H. J.: A Test for the Judgment of Distance, Tr. Am. Ophth. Soc. **17**:195, 1919.

making the target screen more than twice its present size. A shutter just in front of the strips is convenient for controlling the exposures.[8]

My test, of course, does not determine the efficiency of binocular stereopsis under all of the special conditions, including rapid motion, associated with aviation, nor does it determine whether this function is already sufficiently coordinated with the many other functions an aviator will need to employ. No test other than that of actual flying could satisfactorily determine all these facts—the final test of stereopsis adequate for flying lies in the flying. Nevertheless, my test seems to be the best now available for determining as concerns stereopsis a subject's fitness to begin training in aviation or to undertake any vocation in which high acuity and reliability of this function are of great importance.

SUMMARY

A test for grading the acuity of binocular stereopsis is described in which misleading size differences make binocular parallax the only correct evidence of relative depth and cause perception of false depth when this correct evidence is not perceived. This test satisfactorily determines that the subject can rely on the maximum acuity found.

The usual subject has less than one chance in five million of passing the test entirely by guessing, and even a practiced cheater has less than one chance in sixty-five thousand.

The system adopted for grading acuity of stereopsis has not previously been used for this purpose, although it is analogous to the Snellen system for grading acuity of vision.

The test is simple and rapid and is made without the use of a stereoscope or any other viewing instrument. It seems to be the best now available for determining in regard to stereopsis a subject's fitness to undertake aviation or any other vocation in which high acuity and reliability of stereopsis are of great importance.

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ABSTRACT OF DISCUSSION

Dr. M. C. Wheeler, New York: There are few subjects that are of greater interest and importance to ophthalmologists today than the one that Dr. Verhoeff has presented. While tests for binocular stereopsis have wide applications, their use in the selection of candidates for the flying services eclipses all others at this time.

The Howard-Dolman apparatus is too bulky for the office of the average ophthalmologist, who has been forced to rely largely on stereoscopic slides for testing binocular stereopsis and its acuity. Dr. Verhoeff's device should fill an important need, for, in addition to being superior to all other devices, it has the distinct advantage of being compact and simple to operate.

8. I have constructed such an apparatus for the Massachusetts Eye and Ear Infirmary.

I should like to raise one question. Dr. Verhoeff has pointed out numerous theoretic objections to the Howard-Dolman apparatus, which his device corrects, yet I do not believe that he has given any evidence that the results obtained by his method, at distances under 2 meters, will be valid at distances of 6 meters or more. These are the distances at which a pilot must make his accurate estimations of distance. I fully expect that after the proper correlation with actual experience has been made, Dr. Verhoeff's method will prove to be everything that he claims, but from the evidence presented I wonder if his final statement is justified, namely, that "It seems to be the best now available for determinning in regard to stereopsis a subject's fitness to undertake aviation. . . ." In spite of its many deficiencies, the Howard-Dolman apparatus has proved its value on the flying field.

DR. J. B. HITZ, Milwaukee: There has long been a need for a simple, quick, practical test of depth perception which does not utilize the principle of the stereoscope. This instrument, in Dr. Verhoeff's own words, "often seriously interferes with stereoscopic perception."

Dr. Verhoeff's instrument is as simple in construction as it is in operation. Any one with a pair of scissors and a knife can make a good working model in two hours.

My associates and I made a model instrument, following the author's directions, and tested 40 patients with it, at the same time recording the visual acuity, the ocular muscle balance at 6 meters and at 0.3 meter according to the screen test, the near point of convergence and the depth perception according to the Howard-Dolman apparatus.

We encountered some difficulty at first in getting patients to understand what was wanted from the test. This, I believe, is a criticism more of the examiner's command of English or the patient's ability to understand it than of the test itself. Occasional patients would appear at first to judge the depth difference on the basis purely of size of the object, a moment or two later perceiving the true depth difference. In all probability such patients viewed the instrument at first with monocular vision, binocular vision coming into play a few seconds later.

Since it has been well proved that accommodation plays little or no part in depth perception, at least for depth differences as small as 2.5 mm., the use of the test at from 0.5 to 2 meters is in no way an objection.

We were interested in comparing the results of actual tests with the Howard-Dolman apparatus, as this is the only instrument in general use which attempts to grade depth perception quantitatively without the use of the stereoscope.

In using the Howard apparatus we have for some years used Howard's original method, that of having the examiner set the targets under cover, the patient only stating which rod is nearest to him. In order to record a patient's depth perception at a given separation of the rods, fifteen consecutive correct answers are required. This number of checks gives the examinee less than one chance in 34,000 of getting all the answers correct by guess work. The choice of whether the movable rod is in front of or behind the stationary one is left to mathematical chance, shuffled cards being used to determine its position. We used this method rather than that of allowing the patient to

adjust the apparatus himself because, first, it is far simpler to understand, particularly for children, and, secondly, we desired to find the minimal separation at which the patient could constantly judge depth rather than the maximum at which there was no depth discernible.

In comparing the two tests, we found that a comparison of the actual parallactic angles was not possible because of the marked increase in angle for a given depth difference when the distance from the instrument to the eyes was lessened. Therefore, we selected arbitrarily 20/25, or the ability to detect a 2.5 mm. depth difference at 80 cm. on Dr. Verhoeff's instrument and a 35 mm. separation at 6 meters on the Howard apparatus, as critera for passage of the tests. Interpreting our findings on this basis, we found that of our series of 40 patients (1) 30, or 75 per cent, passed both tests, (2) 6, or 15 per cent, failed both tests and (3) 4, or 10 per cent, were inconsistent. Of the 4 last-mentioned patients, the condition of 2 was borderline and 1 had a definite mild myopia accounting for failure in the 6 meter test and success in the 1 meter test. In other words, for the sake of discussion the criteria mentioned being accepted for passage or failure of the two tests, there was a definite correlation in the findings in 90 per cent of the cases.

Calculating the parallactic angles for the two tests (omitting 4 cases in which depth perception was so poor it could not be recorded), we found that the parallactic angles subtended in Dr. Verhoeff's test averaged slightly over four times those in the Howard test. I should like to ask Dr. Verhoeff whether he accounts for this difference by principle of size difference introduced in his test.

Other interesting points in this study might bear further investigation: While there were 8 patients who showed defective vision, heterophoria or poor convergence and passed the depth perception tests, no patient who had normal vision, muscle balance and convergence according to the generally accepted criteria failed to pass the depth perception tests. This would suggest the fact, which I have believed to be true for some time but which I have not seen stated in the literature, that with normal vision and normal extraocular muscle function as tested by accepted methods, poor depth perception is a rare phenomenon. Other factors have been mentioned in the literature which could have an effect on depth perception, namely, (1) hyperopia of sufficient amount to disturb the accommodation-convergence relationship and (2) aniseikonia.

Dr. Verhoeff has presented an extremely valuable instrument which is simple and inexpensive to construct, is quick and easy to use and compares favorably with other instruments, which, while they may not be perfect have stood the test of time as practical and hitherto indispensable instruments.

Dr. Karl W. Ascher, Cincinnati: Binocular instantaneous depth perception does not range gradually from a normal average to zero, as visual acuity does. When a large number of persons are tested by the same method, the thresholds of stereopsis will be close to each other provided visual acuity and muscular balance are normal. While the influence of auxiliary motives may create boundless differences in the judgment of distance, depth perception due to binocular dissimilarity of

retinal images is either present or absent. Its presence can be easily proved by the drop test of Hering. Peas slightly varying in size and falling at a minute distance beyond or in front of the tip of an immovable needle are exposed for fractions of a second. With this test, a 100 per cent of correct answers will be obtained from persons with normal stereopsis. With Dr. Verhoeff's ingenious apparatus, too, the thresholds of numerous persons previously selected for good visual acuity and muscular balance will probably have almost equal top values owing to the fact that the threshold for stereopsis corresponds closely with the threshold for vernier acuity.

Up to this time the methods for testing of depth perception have been based on the highest possible exclusion of auxiliary motives of space localization. In practice, however, just these secondary motives of depth judgment are the only ones available at the distances concerned in practical flying. The accuracy of retinal binocular depth perception drops considerably in the peripheral field, and it falls at an increasing ratio with the absolute distance of the observed object. While, at a distance of 1 meter with a threshold of 5 arc seconds, 0.5 mm. differences are exactly recognizable, at 1,000 meters, only a difference of 274 meters can be appreciated. For these distances, only auxiliary motives of space judgment are of value. Accommodation and convergence, not very efficient at close distances, are of no help whatever at the distances important for flying. The auxiliary motives of distance judgment may vary considerably, while the differences in the threshold of binocular stereopsis are more dependent on the method used and on the differences in function from person to person provided there is normal vision. I wonder whether a flyer attaining 65 per cent in the new Keystone test would be more exact in landing than one with only 60 or 55 per cent.

The evaluation of the auxiliary motives in distance judgment can be obtained by a method based on the fact that equally sized squares exposed at different distances appear to be equal only when their relative and their absolute distance are correctly evaluated by the tested persons. With the utilization of fewer auxiliary motives or with insufficient utilization of them, the influence of the size of the retinal image will increase and the judgment about the apparent size will be led principally by the visual angle. The square comparison test is the only possible test for space judgment for distances beyond 1 mile (1.6 kilometers).

I should like to recommend the square comparison method for examinations of aviators for four reasons:

1. It includes all motives of distance judgment in a subconscious way.

2. It can be used in the central parts of the visual fields as well as in their periphery and even in the temporal crescents of monocular vision.

3. It concerns just the distances at which dissimilarity in the retinal images ceases to be of value.

4. Dissimulation is improbable.

Dr. Walter B. Lancaster, Hanover, N. H.: I wish to discuss Dr. Verhoeff's test from what the lieutenant (Dr. Ascher) spoke of as the pragmatic point of view: not whether this is a good test for stereopsis but whether granted the test is good, it is of value to know the depth perception, for example, of an aviator or of a man who is handling machinery.

Stereopsis gives a keen and accurate estimate of the relative distance of two objects which are fairly closely juxtaposed and not far off. By relative distance I mean the distance of one compared with that of the other. If I look at two pencils side by side rather close together, at a distance of a meter or two, stereopsis will enable me tell whether one is a little farther away than the other (relative distance); but if, instead of being close together, they are widely separated (say 0.5 to 1 meter apart) but still a meter or two from the eyes, stereopsis cannot provide accurate judgment as to which is nearer the eye. Moreover, as to how far both of them are from the person who is looking (egocentric factor of space), stereopsis does not give that kind of important information.

It is not often that persons have trouble with stereopsis when they have good visual acuity and are not suppressing the image of one eye or otherwise avoiding binocular vision. I think the most impressive way to demonstrate this is to show that a person can have considerable abnormal spatial perception and still get perfect stereopsis. With glasses which cause a considerable and obvious distortion of space, one gets perfect stereopsis if one had it to begin with. In other words, stereopsis, as some of the armed forces have decided, is of little value in an estimation of an aviator's capacity for accurate spatial localization.

DR. MORRIS DAVIDSON, New York: I should like to call attention to the usefulness of quantitative depth perception. It is not true that a person either has depth perception or has not got it. A person who has one eye, of course, has not got it. Persons who have two eyes and normal visual acuity in either eye have varying depth perception. What the variations are due to is too difficult to analyze in brief. But one might say that just as normal eyes have visual acuity varying between 20/20 and 20/10, so normal pairs of eyes have a stereoscopic acuity varying between certain limits.

I should also like to point out that there are monocular clues to depth judgment. Therefore, there is a threshold of monocular depth judgment. The smaller the distance at which one tests, the more likely there is to be an approximation between the high threshold of binocular depth perception and the low threshold of monocular depth judgment. Therefore, at less than 2 meters all tests become unreliable.

The optimum range of testing is between 2 meters and 6 meters. I do not believe that the Howard-Dolman method is bad. I think it is an excellent method and based on sound, scientific, physiologic principles.

What is the normal? By practically all methods based on sound, scientific principles, 20 seconds of arc is normal stereoscopic acuity. That is present in 60 per cent of persons with two normal eyes. Therefore, it may be considered as normal. But the quantitative test becomes inaccurate at any distance less than 2 meters, and I do not believe that it should be used at that distance or less if one wishes accurate results.

DR. ROBERT H. PECKHAM, Pensacola, Fla.: A point that has been brought to mind regarding the problem of stereoscopic perception with relation to aviation or any other activity requiring binocular vision is the basic importance of the work at Dartmouth.

Binocular visual orientation includes more than the measurement of a small central area surrounding the point of fixation.

The performance problems required in aviation and in almost every other form of activity in which binocular vision is necessary involve the use of the entire peripheral field. Consequently, a test is necessary for stereopsis, but that test must concern itself with the response as it pertains to the whole field.

The Howard-Dolman test is an accurate, reliable test for the small, central portion of the visual field. The test which Dr. Verhoeff has described is a more reliable, more accurate test for performance in that same small and relatively unimportant area. The major problem is to discover by what means, both eyes being used, one's orientation of oneself with respect to space is accomplished.

I bring up the point in this discussion because I have seen so many tests devised for central stereopsis. There are, perhaps, forty or fifty, and if I had nothing else to do I could devise another forty or fifty. Some of them would not be as good, and most of them would be much poorer, than the one Dr. Verhoeff has presented. But to ophthalmologists who feel it necessary to make a test, let me make a plea that they make a test to determine spatial orientation requiring the use of both eyes.

DR. F. H. VERHOEFF, Boston: My test determines the subject's ability to interpret binocular parallax as relative depth. It seems to me that this ability should be the same at any distance. However, the less the distance at which the test is made, the more importance binocular parallax has over relative size.

As I understand it, Dr. Hitz modified Howard's original test and then compared it with mine. Since the conditions still differed from those in my test it would be expected that the two tests would differ as to the minimum perceptible binocular parallax. This makes evident the importance of standardizing my test. Under certain favorable conditions a binocular parallax of less than 1 second can be recognized as depth, but it would not be practical to employ such conditions in a clinical test.

Dr. Lancaster discussed the difference between absolute and relative depth. My test is for relative depth. He said that the armed forces have found that the test of stereopsis is of little value. He should have said that they have found the Howard-Dolman test to be of little value.

Dr. Ascher brought up the old test of Hering, the falling ball test. This test as ordinarily made is open to serious objections even as a qualitative test and certainly cannot be relied on as a quantitative test.

HEREDITARY CORNEAL DYSTROPHIES

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The study of hereditary corneal degenerations has received considerable clarification by the work of Bücklers.[1] Since 1890, when Groenouw[2] reported the first case, a great many types of familial corneal dystrophy have been described which have differed somewhat in the size, shape and position of the opacities. Most ophthalmologists have agreed with Fleischer[3] that all the conditions described were simply morphologic variations of a single disease. However, in 1938 Bücklers published the results of the detailed investigation of several families including 129 patients in whom these diseases were found, and it is now generally accepted that there are actually three distinct types of hereditary corneal dystrophy, which remain essentially unaltered during their transmission from generation to generation.

It is true that the corneas of certain patients may sometimes resemble those found in patients of a different group, and it is this fact which has caused so much confusion in the past. It has been repeated many times in the literature that the different morphologic variations of the opacities have been seen together in the same eye, in either of the eyes of the same patient or in different members of the same family. For instance, linear and nodular opacities have been seen in the same eye by Judd,[4] Shapira,[5] Maury,[6] Malling[7] and many others. This fact was considered evidence that the two types are related. However, the granular, or crumblike, dystrophy often begins with fine linear opacities, which are later replaced by the typical irregular granules. Another

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1. Bücklers, M.: Die erblichen Hornhautdystrophien, Klin. Monatsbl. f. Augenh. (supp. 3) **101**:1, 1938.

2. Groenouw, A.: Knötchenförmige Hornhauttrübungen (Noduli corneae), Arch. f. Augenh. **21**:281, 1890.

3. Fleischer, B.: Ueber familiäre Hornhautentartung, Arch. f. Augenh. **53**: 263, 1905.

4. Judd, J. H.: Nodular Degeneration of the Cornea, Am. J. Ophth. **16**:310, 1933.

5. Shapira, T. M.: Lattice Type of Corneal Dystrophy, Arch. Ophth. **14**:387 (Sept.) 1935.

6. Maury, F. H.: Pathology of Lattice and Nodular Dystrophy, Am. J. Ophth. **19**:866, 1936.

7. Malling, H.: A Family with Groenouw's Keratitis, Acta ophth. **18**:58, 1940.

reason for confusion is the fact that the lattice-like dystrophy usually has small nodular opacities lying within its reticular structure in the later stages.

Correct diagnosis requires careful study with the slit lamp, and it is often necessary to make repeated examinations of the same patient over a considerable period of time. Cavka [8] has emphasized the value of examining the whole family of each newly observed patient as an aid to comprehension of the primary type of dystrophy with which the patient is afflicted.

An accurate diagnosis is of value in determining the prognosis of the disease, since in the macular type blindness usually results at a relatively early age, while in the others useful vision may be retained for a considerably longer period.

Heretofore no detailed account of Bücklers' [9] classification has appeared in the American literature, so that it seems advisable to include it in this report.

Granular or crumblike corneal dystrophy (dystrophia corneae granulosa) includes Groenouw's nodular corneal opacity (type I), Fleischer's familial corneal degeneration (type II) and many other types.

This form is inherited dominantly and therefore transmitted only by parents having the disease themselves. It begins about the time of puberty with the development of delicate dots and fine radiating lines in the superficial layers of the stroma and in Bowman's membrane. Gradually the infiltrations enlarge, thicken and coalesce into irregular granules, rings, hooks and streaks of whitish color and glassy structure. The particles are sharply limited, and the intervening corneal tissue remains clear, as does a 2 to 3 mm. peripheral zone. Especially in later stages the deeper layers of the corneal stroma may be involved as far as Descemet's membrane. The progress of the disease is usually slow, and moderately good vision often remains in the fifth decade. A disk-like opacity in the center of the cornea is finally formed and slowly increases in extent and in density. The surface is somewhat irregular, and the loss of sensitivity usually roughly parallels the progress of the opacification.

Periods of irritation with recurring erosions which stain with fluorescein may occur and may lead to a faulty diagnosis of herpes or recurrent erosions if the parenchymal changes are not observed.

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8. Cavka, V.: Beitrag zur familiären Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **106**:348, 1941.

9. Bücklers, M.: Die drei Formen der familiären Hornhautentartung und ihre Vererbung, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **51**:73, 1936; abstracted, Arch. Ophth. **18**:331 (Sept.) 1937.

This is the most common type. Bücklers reported 91 cases in four family trees.

Macular corneal dystrophy (dystrophia corneae maculosa) includes Groenouw's nodular corneal dystrophy (type II), Fehr's familial macular corneal degeneration, Fleischer's familial corneal degeneration (type I) and other forms.

This is a recessively inherited disease. For this reason it is frequently difficult to trace the heredity of a given patient, and isolated cases have probably been noted in which the hereditary nature was not suspected. Consanguinity of the parents is a common occurrence. The dystrophy begins during the first decade in the form of a more or less diffuse and rapidly progressive opacity of the whole cornea. Small white dots appear which later enlarge and coalesce to form large nodules. Centrally they lie superficially in the stroma just beneath Bowman's membrane, and they may bulge the epithelium forward. In the periphery they are found almost exclusively in the deeper layers. In contrast to the granular form, the tissue between the nodules and at the periphery is also opacified. Visual acuity suffers in youth, and the patient often becomes practically blind at 30. The corneal sensitivity is greatly reduced.

Thirty-two cases in seven families were reported by Bücklers.

Lattice-like corneal dystrophy (dystrophia corneae reticularis) includes the lattice-like keratitis of Haab, the lattice-like corneal degeneration of Dimmer and other forms.

This is the rarest of the three types of hereditary corneal dystrophy, Bücklers having reported but 6 cases. It is inherited dominantly, and it begins usually at about the time of puberty as a system of double-contoured lines which bifurcate and cross one another in the anterior part of the corneal stroma. The lines have the appearance of fine clefts in the parenchyma and in reflected light have a peculiar glassy aspect. No clear area is left in the periphery. Between the linear opacities lie superficial glassy nodules which may raise the epithelium and cause erosions. The corneal surface becomes irregular, and the visual acuity may be diminished considerably by the third decade. The sensitivity of the cornea is usually greatly reduced. No relationship exists between the opacities and the corneal nerves.

Common to all three types is the simultaneous development of opacities in the two eyes in a more or less symmetric manner. The lesions always involve the parenchyma, and they progress through life unceasingly. Attacks of painful irritation and tearing may sometimes occur in all forms. In contrast to what occurs in real chronic inflammation, no blood vessels invade the cornea. Hence vascularization is not a part of the picture of hereditary corneal dystrophies. Transition

from one fundamental type to another does not occur in a person or within a family.

Various theories as to the causation of these conditions have been proposed. It must be admitted that none is entirely satisfactory or complete. It is fairly generally agreed now that the disease is not a primary degeneration of corneal nerves, since the lesions have repeatedly been shown to have no connection with the nerves or the nerve endings. Tuberculosis has been suggested as the underlying cause, but there is no evidence that it is in most cases. The most likely explanation is that the disease is a primary transmissible degeneration, with the possibility that faulty nutrition may be a contributing factor.

According to the microscopic examination of many small bits of corneal tissue and the examination of a few whole eyes, the chief pathologic change seems to be a hyaline-lipoid degeneration of localized portions of the corneal lamellas. The epithelium and Bowman's membrane may be the seat of similar degenerative changes or may be flattened by the underlying nodules. Bowman's membrane may ultimately be destroyed in the diseased areas.

Treatment of these dystrophies has been unsatisfactory. The maintenence of mild hyperemia with ethylmorphine hydrochloride or by light massage with yellow mercuric oxide may be tried. More vigorous treatment by massage with ethylmorphine hydrochloride and mercury ointment combined with the application of heat, diathermy, etc., has little to recommend it over bland treatment (Duke-Elder [10]). In the later stages improvement in vision may be secured by optical iridectomy in those cases in which enough clear cornea remains in the periphery. A few successful results have been reported after keratoplasty.

All of Bücklers' 129 cases and practically all cases of hereditary corneal dystrophy of the parenchymatous type reported by other authors before 1938 fall definitely into one of the three primary groups. Recently several authors have reported additional cases and confirmed Bücklers' classification.

Bürki [11] reported 3 cases of macular, or spotted, corneal dystrophy and confirmed the recessive inheritance of this type. A transition to other forms of inherited corneal dystrophy was not observed. Consanguinity of the parents existed in 1 case and was not excluded in the other 2. Other hereditary anomalies were also present.

Typical cases of granular corneal dystrophy were observed by Adamantiadis and Djacos.[12] The heredity was dominant. The

10. Duke-Elder, S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1937, vol. 2.

11. Bürki, E.: Ueber fleckige Hornhautdystrophie, Ophthalmologica **98**:311, 1939.

12. Adamantiadis, B., and Djacos, C.: Sur une famille atteinte de dystrophie granuleuse de la cornée, Ophthalmologica **100**:33, 1940.

opacities were located on Bowman's membrane and in the anterior part of the stroma. Transparent corneal tissue lay between the spots, and a transparent ring was left in the periphery. The sensitivity was normal. There was no vascularization, and no reactional phenomena were observed.

Cavka [8] examined a 72 year old man whose corneas were found to contain thin irregular lines and thick curved streaks in the superficial layers of the stroma near Bowman's membrane. All layers of the corneas contained ring-shaped, punctate and crystalline-appearing opacities. The periphery was essentially free from these changes. The corrected vision was normal for each eye. The patient's wife, four children and an uncle had intact corneas. Cavka stated the belief that this case represented an incompletely developed picture of the lattice-like corneal degeneration.

Lloyd [13] saw 4 patients in one family with the typical lattice-like dystrophy. In their cases the formation of painful erosions was an outstanding occurrence. Lloyd found that the daily use of 0.5 per cent solution of mercurochrome prevented the recurrence of the ulcers.

Von der Heydt [14] examined a number of patients representing the various types of hereditary corneal dystrophy, some of whom he followed over a period of several years. He agreed essentially with the classification of Bücklers [9] which had appeared in a preliminary report in 1936.

It has been shown that the more common hereditary corneal dystrophies may be classified into three primary and distinct groups. However, this does not mean that no other forms of this disease exist. Several reports of possibly different types may be found in the literature. A few will be mentioned here.

Schnyder [15] described 4 cases in which crystalline-like opacities had existed in the central part of the cornea since early youth. The opacities lay predominantly in the anterior third of the parenchyma immediately under Bowman's membrane. None of the patients had symptoms of inflammation or other irritation. In all cases there was present within the palpebral aperture on the nasal and the temporal portion of the limbus a white limbus girdle type I of Vogt. According to Schnyder this picture, presented for the first time in 1927, represents a previously unknown type of degenerative corneal disease which is inherited dominantly.

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13. Lloyd, R.: A Family with Lattice Dystrophy of the Cornea, Tr. Am. Ophth. Soc. **37**:120, 1939.

14. Von der Heydt, R.: Corneal Dystrophies: Types, Am. J. Ophth. **20**:738, 1937.

15. Schnyder, W. F.: Scheibenförmige Kristalleinlagerungen in der Hornhautmitte als Erbleiden, Klin. Monatsbl. f. Augenh. **103**:494, 1939.

Reichling [16] described a peculiar type of corneal dystrophy found in two offspring of the union between a degenerate father and his daughter. A concentric ring of dense, superficial, slightly raised opacities in the anterior stratum of the cornea was present bilaterally. A fine yellow stippling existed in the cornea and extended all the way to the periphery.

Pillat [17] described what he thought was a new type of hereditary dystrophy occurring in three generations. The lesions in the cornea consisted of two distinct types, one found in the central area and one in the periphery. Light gray, irregular, circumscribed opacities lay in the deepest and middle layers of the stroma in the central area. The tissue between the spots remained clear and normal. Some of the larger swellings bulged Descemet's membrane into the anterior chamber. The epithelium and Bowman's membrane were uninvolved. The peripheral diseased area contained countless fine glassy lines in the anterior layers of the stroma visible only in the indirect illumination of the slit lamp. The corneal nerves and sensitivity were normal. Vascularization of the cornea was not observed. Attacks of painful irritation did not occur. In spite of the similarity of the central opacities to the granular corneal dystrophy, Pillat stated the belief that this disease is distinguished from the granular dystrophy by the depth and the position of the opacities and by the peculiar appearance of the peripheral areas.

It should perhaps be mentioned that other dystrophies of the cornea, such as the isolated epithelial or endothelial dystrophies and the combined endothelial and epithelial dystrophy of Fuchs, have been thought by some investigators to have a hereditary background. Such a background is not as clearcut as in the conditions under consideration in which the principal lesions are found in the corneal parenchyma. However, Meesmann and Wilke [18] have given a detailed report of a new type of dystrophy of the corneal epithelium which was inherited as a dominant character in 34 persons of two families. The disease began in early childhood as dotted and vesicular opacities in the epithelium with slight roughness of the surface and pain in recurring attacks. It progressed through life, with, however, only moderate visual disability resulting. Only 3 of the patients had involvement of the corneal stroma. This in all probability represents a definitely hereditary dystrophy of the corneal epithelium.

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16. Reichling, W.: Ueber eine noch nicht beschriebene degenerative Hornhautveränderung, Klin. Monatsbl. f. Augenh. **105**:324, 1940.

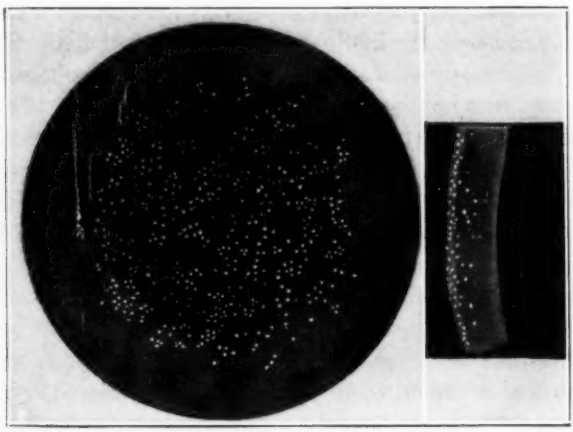
17. Pillat, A.: Zur Frage der familiären Hornhautentartung über eine eigenartige tiefe schollige und periphere gitterförmige familiäre Hornhautdystrophie, Klin. Monatsbl. f. Augenh. **104**:571, 1940.

18. Meesmann, A., and Wilke, F.: Klinische und anatomische Untersuchungen über eine bisher unbekannte dominant vererbte Epitheldystrophie der Hornhaut, Klin. Monatsbl. f. Augenh. **103**:361, 1939.

REPORT OF CASES

The following cases undoubtedly represent early stages of the most common type of hereditary corneal dystrophy, the granular, or crumb-like, form. The corneal lesions were discovered accidentally on routine examination for glasses. Neither of the patients had noticed any loss of vision, nor had they suffered any attacks of painful irritation.

CASE 1.—A 24 year old medical student had been wearing a rather high cylindric correction since the age of 6, and he came to the clinic for a routine check of his glasses. His general health was good. Corrected vision was 20/25 in each eye. External examination and examination of the pupils, disks and fundi gave negative results, but when the examiner looked through a +20 lens in the ophthalmoscope he saw that the cornea was somewhat hazy. Under the slit lamp the cornea was found to contain many minute, grayish white, irregularly round



The right cornea of patient 2. The other corneas were similar.

opacities in the superficial part of the stroma and epithelium adjacent to Bowman's membrane. The spots extended almost to the limbus but were more numerous in the central area. The corneal tissue between the lesions was clear. Corneal nerves were not seen. A few deep vessels crossed the limbus nasally in each eye, but these extended only a few millimeters into the cornea and were thought to be insignificant.

CASE 2.—A 22 year old law student, brother of the first patient, was in good general health. His corrected vision was 20/30+ in each eye. External examination and examination of the pupils, disks and fundi gave negative results. The slit lamp revealed a picture similar to that in the first case. Rather evenly spaced white flecks lay in the epithelium and superficial layers of the stroma bilaterally. A definite clear area was present in the periphery. There was no vascularization of the cornea.

Examination of other members of the family of these patients has not been possible. Such an examination, of course, would be desirable,

as has been mentioned previously. However, there can be little question of the diagnosis in these cases when the appearance of the corneas is compared with the drawings of the corneas in the cases described by Bücklers and others. The course of the disease is relatively benign, and, although gradual progression of the lesions is to be expected, the prognosis in general is good. Considerable vision should be retained perhaps throughout life.

SUMMARY

The confusion which had previously existed regarding the classification of hereditary corneal dystrophies involving the parenchyma was largely eliminated by the work of Bücklers.

Three forms of dystrophies have been definitely established: (1) a dominant granular, or crumblike, form, (2) a recessive macular type and (3) a dominant lattice-like type.

Other, rarer types of hereditary dystrophy of the cornea undoubtedly exist. A few instances have been reported.

Two cases are reported as representing an early stage of the granular, or crumblike, dystrophy.

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RESULTS OF DESENSITIZATION IN TUBERCULOUS IRITIS

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There is experimental evidence to show that the uveal tract can be sensitized by intraocular injection of protein, so that on later parenteral injection of the same kind of protein a reaction is set up, with redness and exudate in the previously treated eye.

In certain cases of recurrent iritis, in which there is no other demonstrable locus of infection, the administration of tuberculin in appropriate doses gives rise to a local (skin), general and focal (eye) reaction.

It has been assumed that the uveal tract is sensitized to products of the tubercle bacillus, so that it reacts to relatively small amounts of these products when they are formed and liberated within the body or are introduced into it artificially.

If in some way the sensitiveness of the body, including the tissues of the uveal tract, could be reduced, it might be possible to lower the threshold of explosion, so that reactions would not occur in response to such stimuli as arise in subjects with recurrent iritis.

Many attempts at immunization with tuberculin have been made. These have always failed in both man and experimental animals. Tuberculin has, however, been used in the treatment of tuberculous lesions of the eye, on the theory that desensitization of the body, including the tissues of the uveal tract, is thereby produced. Such treatment in certain instances has been believed successful.

The present report concerns an attempt at desensitization by a different method. Observations were made in 2 cases of recurrent tuberculous iritis in which the inhalation of fumes from saline suspensions of dead tubercle bacilli was followed by a definite reduction of sensitivity as determined by periodic titrations with dilutions of tuberculin administered intracutaneously. One patient has remained

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free from recurrence of the iritis from the institution of treatment in 1940 to the time of writing. The second patient remained free from recurrence from the beginning of treatment, in November 1940, to April 1942. He then resumed inhalations and himself devised an inhalation mask which covered the entire face instead of only the nose. The eyes were then directly exposed to fumes, and two days later there was a slight recurrence in the left eye, with conjunctival redness in both eyes. This subsided in three days.

Two cases and two years are too small numbers on which to base any final conclusion. Observations on animals and on other forms of tuberculous infection in man, however, lend additional weight to these observations, which we believe may turn out to be of significance in the relief of tuberculous iritis. For the present we attempt only to report what we have observed.

The method under consideration was discovered accidentally. In the Tice laboratory of the Municipal Tuberculosis Sanitarium of Chicago, whose function it is to prepare and administer the BCG vaccine (bacillus of Calmette and Guérin, an avirulent tubercle bacillus), it was noted that in certain members of the laboratory staff symptoms periodically developed varying from malaise to chills, fever (a temperature up to 104 F.), a tickling sensation in the posterior part of the pharynx, cough, vomiting, headache and backache. After several months, such attacks lessened and finally abated in these persons. The possibility that the symptoms might be related to something happening in the laboratory, possibly a generalized reaction to tuberculin, was suspected for the first time when in a new member of the staff who reacted to 0.00001 mg. of old tuberculin, a similar syndrome developed. It was noted further that the illnesses had a periodicity corresponding to that of certain laboratory procedures concerned in the boiling of old cultures and the preparation of vaccine. (It has since been learned that other laboratories have noted similar unexplained illnesses in their personnel.) In the persons affected, previously positive reactions to tuberculin tests were decreased.

It was inferred that the issuing vapors might be the causative agent, and in order to substantiate or refute this assumption, animal experimentation was undertaken. (The following experiments were planned and carried out by S. R. R., who reported on them at Boston on April 2, 1942.[1])

Fumes from a boiling suspension of dead tubercle bacilli in physiologic solution of sodium chloride were allowed to enter a sealed box in which guinea pigs were placed. Visible vapors permeated the enclosure throughout the periods of

1. Rosenthal, S. R.: Proc. Federation Am. Soc. Exper. Biol. **1**:182, 1942.

exposure. The time of exposure for animals which reacted to tuberculin (after intraperitoneal injection with BCG vaccine) was one minute the first day, increasing by one minute daily until sixty minutes was reached. The length of exposure to the vapors at one period was never over fifteen minutes (to prevent suffocation). Tuberculin testing was performed at regular intervals, old tuberculin and purified protein derivative being used.

In these experiments, in which more than 100 animals were used, the following observations were made: In guinea pigs previously made reactive by the injection of avirulent tubercle bacilli, the cutaneous response to tuberculin was appreciably reduced by daily exposures to (1) fumes of boiling salt solution suspensions of tubercle bacilli, (2) sprays of heat-killed bacilli and (3) fumes of boiling suspensions of tubercle bacilli passed through a fritted glass filter (to trap the bacilli in case they issued with the vapors), in the order mentioned. This reduction in reactivity was such that there was noted no response to 1 mg. of old tuberculin (controls, 2 plus to 3 plus) after two to four months of daily exposures. Vapors of old tuberculin or of salt solution did not affect the reactivity to tuberculin. Six months after cessation of treatment the response to tuberculin increased in the animals under study, but as a rule it remained inferior to that of the controls.

Of special interest are the results of the testing of the technician who administered the treatments to the guinea pigs and was exposed to the fumes. At the outset he reacted to 0.001 mg. of old tuberculin (1 plus), but after eight months of exposure he responded but slightly to 1.0 mg. (1 plus). After the summer months, during which the experiment was discontinued, he reacted to 0.2 mg. The technician who boiled the glassware reacted to 0.5 mg. of old tuberculin (1 plus), while her supervisor, who also substituted when the former was ill or on vacation, responded to 0.5 mg. (2 plus). Unfortunately, no previous tuberculin tests on these persons had been made. They had moderate to severe symptoms resembling a generalized reaction to tuberculin when they were first exposed to the fumes of the boiling cultures of vaccine, but later they became symptom free on exposure in the same work. (Two and a half years after the first test, the technician does not react to 1.0 mg. of old tuberculin.)

The agent responsible for the decrease of sensitivity is not known. That some volatile substance may play a role is suspected. The distillate from boiling tubercle bacilli passed through a fritted glass filter has the following properties: It does not contain demonstrable tubercle bacilli (centrifuging for one to three hours); it does not neutralize the action of tuberculin or call forth a cutaneous response in guinea pigs that react to tuberculin (filtrate concentrated thirty times); when

injected into normal guinea pigs it alters the reactivity to tuberculin after a delay of three to ten months (this effect is unexplained and requires further study).

CASE 1.—*History and Examination.*—L. C., a white man aged 24, a teacher, entered Presbyterian Hospital July 15, 1940.

In 1936 he had had iritis in the left eye, with subsequent attacks at intervals of three to six months. In all there had been some thirteen attacks in one or the other eye; the present attack had lasted two months.

In addition to the iritis, there had been several attacks of persistent diarrhea. Roentgen examinations had disclosed no lesion of the bowel. The stools had contained no pus or blood. The mucosa had been found normal on sigmoidoscopic examination. The tonsils had been removed. A recent attack of diarrhea had subsided with use of a low residue diet.

A detailed inquiry disclosed no other facts of significance in relation to the disease of the eye. Physical examination disclosed that the young man was well nourished and of ruddy complexion. There was no evidence of disease in the nose, sinuses or ears. The tonsils had been removed. The lungs, heart, abdomen and prostate were normal. There was no evidence of infection in prostatic strippings.

The urine was normal. The hemoglobin content of the blood was 90 per cent. A blood count showed red cells 4,640,000 and white cells 8,600, with a differential count of polymorphonuclear neutrophils 43 per cent, lymphocytes 57 per cent, monocytes 3 per cent, eosinophils 3 per cent and basophils 1 per cent. Values for the basal metabolic rate were +7 and —4. The Wassermann reaction was negative. A roentgenogram of the chest showed the lung fields and the heart shadow within normal limits and the diaphragm shadows clear. (Roentgenograms of the chest taken after tuberculin tests and later during and after treatment revealed no change.)

Roentgenograms of the dorsal portion of the spine (taken on account of recurrent backache) showed slight lipping of the margins of the midthoracic vertebrae, but no other lesion of bone. Reflexes except those of the eyes (atropine sulfate) were normal.

Summary of Attacks.—Of the attacks which the patient could recall, or of which he had records, there were three or four in the summer of 1936, each lasting three to four days and all in the left eye. In April 1937 there was a severe attack in the left eye lasting two weeks and accompanied by severe pain in the left scapular region. This attack subsided about May 1, after an injection of milk.

In 1938 there was an attack in the right eye. In January 1939 there was a severe attack in the right eye, for which the patient entered another hospital, where he remained two months.

On Oct. 15, 1939 a severe attack began, lasting eight days. A mild attack in the right eye, which began November 11, lasted four days.

On May 23, 1940 a severe attack in the left eye began. This lasted ten days, and the patient reentered a hospital, where he was exhaustively examined for infection which might be related to the iritis, without discovery of any local lesion. A severe attack in the left eye, which lasted eight days, began June 6. A severe attack in the right eye began June 21, and he was readmitted to a hospital on June 27 with bilateral iritis. At this time achlorhydria and slightly prolonged elevation of the blood sugar in a dextrose tolerance test were found, but no further evidence of infection related to the iritis.

The patient entered the Presbyterian Hospital July 15 with severe iritis in the right eye.

Tuberculin Tests.—There was a von Pirquet reaction with a 1.0 by 1.5 cm. zone of redness and slight edema after forty-eight hours. Mantoux tests with 1 : 100,000, 1 : 10,000 and 1 : 1,000 dilutions of old tuberculin gave strongly positive results, with itching of the lesions. There were slight hyperemia of the right eye, some aching over the body, loss of appetite and a temperature of 99.6 F. by the third day, with no pain in the eyes.

Three days later, July 21, 3 mg. of old tuberculin was given subcutaneously. During the following night and day there was a general reaction, with aching over the body, slight vomiting, a temperature of 101 F. and a rise in the pulse rate from 80 to 100 per minute. There was pain in the eyes, with circumcorneal injection to a marked degree in the right eye and to a less degree in the left eye. There was a pronounced recrudescence of redness at the sites of the Mantoux tests. This reaction subsided on the following day. These reactions were interpreted as definitely positive local and general reactions and focal reactions in the eyes. By July 26, the circumcorneal injection had subsided and the redness at sites of the Mantoux tests was fading.

Ocular Findings.—On July 12 there was moderate ciliary and conjunctival redness of each eye, more marked in the right; the tactile tension was slightly low, and the pupils were round and even and without synechias and dilated to 8 mm. The posterior surface of the right cornea had many fine and a moderate number of larger precipitates, some of them brownish in color; the slit lamp showed 2 or 3 cells per field; the iris and the lens were normal. The left eye showed only an increased density of the aqueous ray. The corrected vision was 1.5 — 2 in the right eye and 1.2 — 2 in the left.

The diagnosis was recurrent bilateral iridocyclitis serosa. By August 19, with the patient under local and general treatment all evidence of active iridocyclitis, including the clouding of the aqueous ray, had subsided in each eye.

The history, examination and tests disclosed no local infection and no cause for the iritis other than the evidence of the positive reactions to tuberculin tests. A diagnosis of recurrent tuberculous iritis was made. There was no evidence of active tuberculosis in the lungs or elsewhere in the body. This patient had suffered some thirteen attacks of iritis beginning in 1939 and varying in number from one to four each year. In 1940 he had four attacks up to July and was still suffering from the last attack when he came under our observation in that month.

Treatment by Inhalation of Fumes from a Suspension of Dead Tubercle Bacilli (BCG).—In planning inhalation treatment in this first case of iritis we had no experience to guide us, other than that with animals (guinea pigs), in which there had been no serious reactions, and that with certain human patients, in whom preliminary trials had produced no permanent untoward results. Also, we knew that in both man and experimental animals repeated inhalations resulted in a reduction of sensitiveness to tuberculin as shown by cutaneous tests. It seemed possible that if a moderate reduction in sensitiveness to tuberculin could be brought about in the patient with iritis, the

sensitiveness of the uveal tissue might be reduced so that iritis would not recur.

The suspension of dead tubercle bacilli (BCG) was furnished in a small 500 cc. Florence flask which contained about 200 cc. of a suspension of bacilli in salt solution (5 mg. per cubic centimeter). The patient breathed the air of the flask through a small funnel on the first two days for ten seconds, on the next two days for thirty seconds and on the next four days for sixty seconds. On the next day the flask was heated to 40 C., and the patient took one whiff; on succeeding days the breathing time was increased gradually to sixty seconds; the flask was then heated to 100 C., and the time of breathing was increased from ten seconds to two minutes by the fifth day. By August 24 the fumes were being inhaled from the gently boiling suspension for twelve minutes, and by September 5 (date of discharge from the hospital) the duration of inhalation was thirty minutes. This treatment was continued thirty minutes daily at home until May 8, 1941.

Mantoux tests were made at intervals of approximately one month while the patient was in the hospital and at somewhat longer intervals during 1941 and 1942.

The sensitiveness to cutaneous tests decreased after November 1940 and was maintained at a lower level until November 1941. During the treatment in the hospital the patient was observed each day for any possible reaction, but no symptoms were noted which could be interpreted as related to treatment. Viewed in retrospect, treatment in the early weeks was conducted with unnecessary caution, but it will be appreciated that in this first case we had little information as to the potency of the agent with which we were dealing.

On July 28, 1940, during the period of observation in the hospital, the instillation of atropine sulfate was reduced from three times to once a day, and on August 1 there was a slight circumcorneal redness, which disappeared on the following day. This was interpreted as due to too early withdrawal of atropine.

Aside from this incident, there has been no recurrence of iritis in twenty-two months. The patient is in excellent general health.

CASE 2.—*History and Examination.*—L. J. S., a white man aged 40, a salesman, entered Presbyterian Hospital June 20, 1940 suffering from pain above and in the right eye, with photophobia and circumcorneal hyperemia. Such attacks had occurred at irregular intervals of a few months to a year since 1929, usually following periods of strenuous work or nervous strain. They had usually involved the eyes separately, affecting the left somewhat more often than the right.

The patient had been repeatedly examined for any infectious cause; the tonsils were removed in 1930. No infection had been found in the teeth, sinuses or prostate. The Wassermann reaction was negative. The spinal fluid was normal. The general health was good, with a tendency to gain weight. Until a year before the patient had been subject to severe pain low in the back. At 8 years of age he had pneumonia following empyema which required drainage. Various treatments of the iritis included fever therapy with typhoid vaccine and use of sulfanilamide, without permanent benefit.

Examination disclosed that the patient was well developed, well nourished and apparently younger than the stated age. The height was 69 inches (175 cm.) and the weight 174 pounds (79 Kg.). There were a fading hyperemic rash over the back (said to have appeared after treatment with sulfanilamide) and a healing

herpes of the upper lip, which had appeared after administration of typhoid vaccine five days previously. There was an old scar from a rib resection over the right lower part of the chest in the axillary line at the level of the eighth interspace. The remainder of the examination disclosed no evidence of infection.

The tonsils had been cleanly removed. The heart, lungs, abdomen, rectum, prostate and extremities were normal. The hemoglobin content of the blood was 100 per cent. A blood count showed red cells 5,370,000 and white cells 11,200, with a differential count of polymorphonuclear neutrophils 58, mononuclears 35, eosinophils 6, basophils 1 and platelets normal. The Kahn reaction was negative. The urine was normal. The blood chemistry was normal. A roentgenogram of the chest showed a normal heart shadow, lung fields within normal limits and a small adhesion at the right costophrenic angle. (A roentgenogram of the chest taken five months later, after the tuberculin tests and treatment for one month, showed no change.) Roentgenograms of the sinuses showed normal conditions, as did cholecystograms. Roentgenograms of the spine disclosed some scoliosis of the thoracic and lumbar portions and increased density of the sacroiliac joints, with no other bone change. No infection which could be related to the iritis was found.

Ocular Findings.—On June 19, 1940 a large gelatinous exudate was present in the lower temporal third of the right anterior chamber. The pupil measured 5.5 mm. and was round; the tactile tension was full. There was a mixed conjunctival and ciliary injection with a tendency to chemosis of the conjunctiva. The anterior capsule of the lens showed a number of brown accretions. There was considerable ciliary tenderness, and lacrimation and photophobia were present. The left eye was normal. The corrected vision was 0.1 in the right eye and 1.2 — 4 in the left. Five days later blood was added to the exudate in the anterior chamber and the tension was + 3; the use of atropine sulfate was stopped, and after two days of administration of epinephrine hydrochloride the tension was normal and four fifths of the blood and three fourths of the exudate had been absorbed. The blood and the exudate continued to be absorbed and the use of atropine was resumed in a few days. Recurrent exudative iridocyclitis of the right eye was diagnosed.

On July 11 examination disclosed that improvement had continued, and no lacrimation or photophobia remained. The corrected vision in the right eye was 0.6 — 3. Only slight ciliary injection was present.

On December 3 the patient reported that a two day attack of iritis had occurred late in August. Each eye was now white; the pupils, which measured 4 mm., were round and even. There were no precipitates on the back of either cornea, and the aqueous ray was normal on slit lamp examination. The tactile tension was low (right eye 12.5, left eye 9). The right iris had a slight thickening anterior to the sphincter at 6 : 30 o'clock. The corrected vision was 1.5 — 4 in the right eye and 1.5 — 3 in the left.

The diagnosis was recurrent serous iridocyclitis of the left eye.

Tuberculin Tests.—A preliminary von Pirquet test gave a doubtful reaction. It was later found that the test had been made in error with a highly dilute solution of tuberculin. The site of the test showed a pronounced reaction after subsequent tuberculin tests.

Mantoux tests with 1 : 100,000, 1 : 10,000 and 1 : 1,000 dilutions gave strongly positive local reactions, as did a subcutaneous injection of 1 mg. of old tuberculin.

There was a pronounced exacerbation of redness in the eye, with severe pain requiring morphine, but no febrile reaction beyond a rise in temperature to 99 F.

From the history, examination and tuberculin tests with strong local and focal (eye) reactions, a diagnosis of recurrent tuberculous iritis was made. The iritis subsided, and the patient left the hospital, to return later for treatment.

During the following month there was a slight recurrence of iritis in the left eye, which lasted only a few days.

The patient reentered the hospital November 4 for treatment. Reexamination disclosed no new evidence of infection. The eyes were quiet. Mantoux tests with 1:100,000 and 1:10,000 dilutions of old tuberculin gave local reactions slightly more pronounced than those of June with corresponding dilutions. There was no focal reaction in the eyes.

Treatment.—The fumes from a suspension of dead tubercle bacilli in salt solution (5 mg. per cubic centimeter) were inhaled for ten minutes twice on the first day; during the second day fumes from the flask warmed to 40 C. were twice inhaled for ten minutes. During the third day the vapor from the flask heated to 100 C. was twice inhaled for ten minutes. Thereafter the period of inhalation was increased by two minutes daily until by November 23 the period of inhalation was thirty minutes twice daily. This was continued until December 5, when the patient left the hospital, to continue the inhalations at home.

Mantoux tests on December 2 gave less marked reactions than those of November 6. Inhalations were continued until May 9, 1941.

On July 22, 1940, although the left eye had been slightly red for ten days, the slit lamp showed only 3 to 4 cells per field and only the faintest increase in density of the aqueous ray. This condition had followed exposure to fumes of turpentine in painting. The vision in this eye was 1.5 — 4.

On July 31, 1941 there had been no injection for the past six days.

On August 8 the patient reported no recurrence of inflammation in either eye.

By October 23 the reactions to the Mantoux tests were much less pronounced, especially as regards edema and itching of the lesions.

On April 4, 1942 the reactions to the Mantoux tests were of approximately the same degree as those of Oct. 23, 1941. There had been no recurrence of iritis, although the patient had been working hard. On April 17, after resuming inhalation treatment, he exposed the eyes directly to the fumes. This procedure was followed in two days by recurrence of redness in both eyes and an iritis in the left eye which subsided after three days.

GRAPHIC REPRESENTATIONS OF CHANGES IN SENSITIVITY

An attempt has been made to record the degrees of reaction by (1) the size of the papule at the site of injection, (2) the degree of edema or vesiculation of the lesion, (3) local itching and (4) the extent of the areola of hyperemia surrounding the lesion. All these changes are concerned in an estimate of the degree of reaction. The diameter of the central papule is best suited to graphic records but in patients gives an incomplete picture of the degree of reaction.

The accompanying charts record the reactions in guinea pigs immunized with BCG vaccine and then treated with fumes from tubercle bacillus suspensions and in the 2 patients as gaged by the diameter of the papules resulting from Mantoux tests.

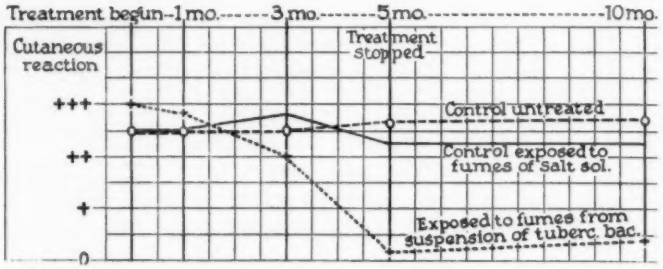

Chart 1.—Effect on the reaction to tuberculin in guinea pigs immunized with BCG vaccine of exposure to the fumes of a suspension of tubercle bacilli in salt solution. The degree of cutaneous reaction to tuberculin as expressed on the left of the chart was estimated on the basis of the several factors of the reaction, including diameter of the papule, edema and vesiculation. If a chart is constructed on the basis of diameter of the papule alone, similar curves are obtained.

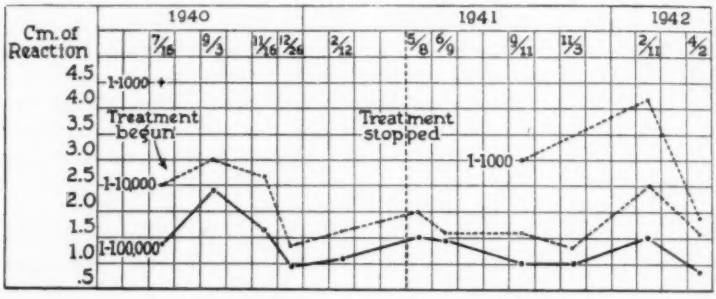

Chart 2 (case 1).—The degree of cutaneous reaction to old tuberculin after intradermal injections of 0.1 cc. of the dilutions indicated, recorded by the diameter of the papule in centimeters. This is a convenient method of graphic representation but does not give a complete indication of the degree of reaction. The reactivity to tuberculin decreased after the inhalations of fumes from heated suspensions of dead tubercle bacilli in saline solution.

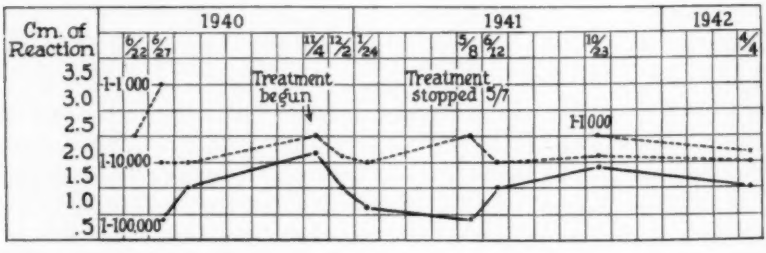

Chart 3 (case 2).—The degree of reaction to intracutaneous injections of old tuberculin in the dilutions indicated, before and after inhalations of fumes from heated suspensions of dead tubercle bacilli in salt solution. The decrease in reactivity as expressed by the total reaction, including all factors, was somewhat greater than that indicated in the chart.

SUMMARY

Fumes from salt solution suspensions of dead tubercle bacilli have been observed to produce systemic reactions in man. After long exposure cutaneous reactions to tuberculin are decreased. In guinea pigs immunized with BCG vaccine and then exposed to the fumes, the cutaneous reaction to tuberculin is decreased.

Two patients with recurrent serous iritis of four and thirteen years' standing, respectively, were treated by inhalations of fumes from suspensions of dead tubercle bacilli in salt solution. One patient experienced a reduction of cutaneous sensitiveness to tuberculin and freedom from iritis which has lasted to the time of writing (twenty-six months). The second patient was free from recurrence for seventeen months; then, after a direct prolonged exposure of the eyes to the fumes, there was a slight recurrence lasting three days.

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CATARACT IN RATS FED A LOW PROTEIN DIET

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Galactose cataract in rats was first reported by Mitchell [1] and confirmed by Yudkin and Arnold [2] and Day.[3] The problem was studied from several points of view by Mitchell and Cook.[4] They recorded that galactose cataract develops most easily in young rats. The susceptibility of different strains was analyzed. The sugar content of the blood and of the urine, the influence of protein factors in the diet, changes in other factors and the stages in development and regression of the cataract were problems particularly considered. According to Mitchell and Cook a low protein ration shortened the time of development of the opacity in the lens. On the other hand, a high protein ration tended to retard this pathologic change. Bellows [5] pointed out the inhibitory effect of 0.3 per cent cystine added to a low protein diet containing 35 per cent of galactose. Only slight protection of the eyes was observed by Mitchell and Cook even when larger amounts of that amino acid were used.

In 1940 Mitchell, Cook and Henderson [6] found that enzymic casein hydrolysate had the same protecting role observed in the commercial casein toward galactose cataract. Neither cystine nor methionine offered protection. Urea and choline did not present any anticataractogenic

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1. Mitchell, H. S.: Cataract in Rats Fed on Galactose, J. Nutrition (supp.) **9**:14, 1935; Proc. Soc. Exper. Biol. & Med. **32**:971, 1935.

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3. Day, P. L.: Blood Sugar in Rats Rendered Cataractous by Dietary Procedures, J. Nutrition **12**:395, 1936.

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5. Bellows, J. G.: Biochemistry of the Lens: IX. Influence of Vitamin C and Sulfhydrils on the Production of Galactose Cataract, Arch. Ophth. **16**:762 (Nov.) 1936.

6. Mitchell, H. S.; Cook, G. M., and Henderson, M. D.: Anti-Cataractogenic Action of Certain Nitrogenous Factors, Arch. Ophth. **24**:990 (Nov.) 1940.

property. Finally they recorded that deaminized casein had a stronger protecting capacity and heated casein a lower protecting capacity than commercial casein.

In 1941 Henderson and Mitchell [7] performed new experiments, studying the effect of exposure to dry heat on the growth value and the anticataractogenic property of several proteins. They verified that the protective effect was not correlated to the growth-promoting capacity.

In all the experiments presented by the authors cited the opacity of the lens was induced by either galactose or lactose. Several factors were considered to be interfering in the incidence and in the rate of the development of the lenticular changes.

METHOD

In our experiments cataract was not induced by galactose, as this carbohydrate was never used in the diet. Cataract was recorded in rats used in experiments performed in a study of the relation between growth and the storage of protein by the liver.

Campos and Cavalcanti [8] studied the capacity of the liver to store proteins, and Campos [9] observed its relation to the growth curve of growing rats.

The following diet was used:

	Percentage
Commercial casein	10.0
Starch	64.0
Butter	15.0
Dry yeast	5.0
Salt mixture (Mendel-Osborne)	4.0
Cod liver oil	2.0

Several young rats received this diet for six months. The growth curves were not bad, and they did not present any particular change. Two of them were placed in a separate cage (rat 1417, a female, and rat 1416, a male). From them 4 rats (rats 1546, 1547, 1548 and 1549) were born in normal condition, and nothing was recorded during the weaning period. They were fed normally by the mother. When they were more than 2 months old a change in the lens was recorded.

REPORT OF EXPERIMENTS

RAT 1546.—A cataractous change was first recorded when the animal was 63 days old (May 10, 1941). Slit lamp observation revealed slight nuclear opacity

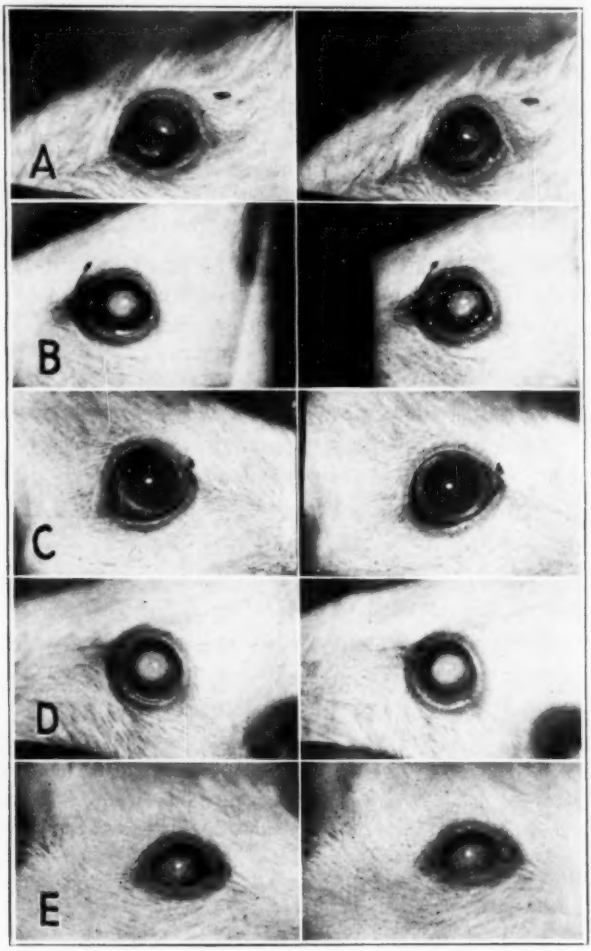
7. Henderson, M. D., and Mitchell, H. S.: The Effect of Dry Heat upon the Anticataractogenic Quality of Certain Proteins, J. Nutrition **21**:115, 1941.

8. de Moura Campos, F. A., and Cavalcanti, T. A. de A.: Considerações sobre o valor nutritivo da proteina de ervilha: Papel do figado na formação de depositos de proteina, Hospital, Rio de Janeiro **13**:247, 1938.

9. de Moura Campos, F. A.: L'immagazzinamento di proteine da parte del fegato, Arch. di sc. biol. **24**:500, 1938.

in each eye. A similar aspect was seen five and thirty days later. Before the second slit lamp observation, a stereoscopic photograph (*A* in the accompanying illustration) was taken. The growth curve was poor.

Rat 1547.—An opacity of the left lens was seen by the naked eye when the animal was 51 days old. Slit lamp observation (May 5, 1941) showed in the right



Cataractous changes in the eyes of rats fed a low protein diet. *A*, rat 1546; *B*, rat 1547; *C*, rat 1548; *D*, rat 1549, right eye; *E*, rat 1549, left eye.

eye an opacity in the center of the lens, the cortex being free, and in the left eye a flower-shaped opacity, the middle part and the cortex being free. A similar condition was observed five and thirty days later, when new slit lamp observations were made. The growth curve was poor.

Rat 1548.—A slight central opacity in the left eye was recorded when the animal was 67 days old. A similar condition was found twenty-five days later. No vessels were visible in the iris. The growth curve was poor.

RAT 1549.—A cataract was seen by the naked eye April 25, 1941, when the animal was 52 days old. The first slit lamp observation was performed May 5. Complete dilatation of the left pupil was not observed in spite of the fact that atropine sulfate had been used four times. There were vessels in the iris, especially radially. A nuclear opacity reached the cortex, as shown in *D* in the accompanying illustration. The right pupil was in almost the same condition as the left. The nuclear opacity of the lens is shown in *E* of the illustration. New observations with the slit lamp were done five and thirty days later, and similar results were recorded. The growth curve was bad.

COMMENT

In our experiments cataractous changes were observed in rats fed a low protein diet (casein 10 per cent). Galactose was not used. Starch was the only carbohydrate food in the diet, which was complete with respect to vitamins, fat and salts. The low protein content was therefore the only dietary factor which may have interfered in the lenticular changes. In normal amounts proteins display a protective action on the eyes. An anticataractogenic property toward galactose cataract was recorded by Mitchell and co-workers. In our experiments lenticular changes were not induced by galactose but possibly by the low protein content of the ration.

SUMMARY

Experiments were performed with albino rats in order that the effect of a low protein diet on the growth might be studied. The ration was given to the parent rats and to the young rats.

Cataractous changes of the lens appeared when the animals were approximately 2 months old. Several changes were observed either by the naked eye or with the slit lamp.

All the animals presented a poor growth curve. Galactose was not used in the diet to induce cataract. The low protein content must be considered in order to explain the appearance of the opacity of the lens.

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ADIE'S SYNDROME (PUPILLOTONIC PSEUDOTABES)

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In 1932 Adie [1] described a syndrome consisting of tonicity of the pupils and absence of tendon reflexes. This syndrome manifests itself in several clinical forms, which are referred to as complete and incomplete. The complete form is characterized by the presence of the tonic convergence reaction in a pupil apparently inactive to light and by absence or diminution of one or more of the tendon reflexes of the lower limbs. The incomplete forms exhibit (1) the tonic pupil alone, (2) atypical phases of the tonic pupil alone, (3) atypical phases of the tonic pupil with absence of tendon reflexes and (4) absence of tendon reflexes alone.

No hereditary or acquired morbid factor is known to play any part in production of the syndrome. In particular there is said to be no relation to syphilis. The syndrome runs a benign course without the addition of further symptoms and is compatible with long life.

Adie's publication gave rise to a large literature, which was summarized by Jelliffe [2] in 1933. The French literature and points of view were summarized by Alajouanine and Morax [3] and the German literature by Kehrer.[4] All the authors mentioned, and particularly Adie himself, emphasized the tonic or myotonic pupillary reactions, which were first described as far back as 1902 by Saenger and by Strasburger independently. Those cases in which the tonic pupillary reactions were found in combination with an absence of tendon reflexes were considered as syphilitic in origin, instances either of congenital tabes or of incipient tabes dorsalis.

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2. Jelliffe, S. E.: Myotonic Pupil: Contribution and Critical Review, J. Neurol. & Psychopath. **13**:349, 1933.

3. Alajouanine, T., and Morax, P.: La pupille tonique (pupillotonie) et ses rapports avec le syndrome d'Adie, Ann. d'ocul. **175**:205, 1938.

4. Kehrer, F.: Die Kuppelungen von Pupillenstörungen mit Aufhelung der Sehnenreflexe: Adie-Syndrom, Pupillotonie, Pseudotabes; konstitutionelle Areflexie, Leipzig, Georg Thieme, 1937.

In 1929 Behr emphasized that pupillotonia, whether in the presence or the absence of ankle jerks, does not justify a diagnosis of syphilis.

In 1924 Foster Moore described pupillotonia superficially resembling the Argyll Robertson phenomenon and occurring in nonsyphilitic subjects.

In 1926 Weill and Reys gave a fairly full description of Adie's syndrome, which they considered to be of infectious origin, and they emphasized the role of sympathetic factors for the pathogenesis of the syndrome, just as did Behr, who attributed them to a peculiar disturbance of the function of the vegetative portion of the third nerve nucleus.

Adie described the pupillotonic phenomena in their most characteristic form as being unilateral, with the tonic pupil considerably larger than the nontonic pupil. About 80 per cent of the patients are female, a large proportion of them young women. Generally the tonic pupil is oval, with either vertical or horizontal orientation. To the usual bedside tests the reaction to light direct and consensual is completely or almost completely absent. When in darkness for nearly an hour the pupil dilates, and when the patient comes into bright light a sluggish contraction may be observed after an interval, so that the pupil becomes narrower than it was before it was in darkness. Contraction becomes more and more sluggish, but the pupil becomes abnormally small, even narrower than the other. Contraction continues even after the convergence impulse has ceased, and redilation begins only some seconds later. Dilation itself is sluggish, and the pupil often requires several seconds to attain normal size.

According to Adie the tonic pupil dilates well in response to mydriatics and contracts with physostigmine. Changes in size from time to time, often through a wide range, are common; they were said by Adie to be an important diagnostic feature. Moreover, the reactions often vary in the same eye at different times.

All degrees of modifications of these characteristics are to be found in atypical cases. There are cases in which pupillary contraction is incomplete. In some, convergence is normal but is followed by retarded dilation. In others convergence contraction may be tonic on one side and absent on the other. There are even cases in which on one side (or on both) the pupil is fixed even to light and on convergence. Although the typical cases are well characterized, in atypical cases all the modifications observable in pupillary disease both of syphilitic and of other causation may be exhibited.

Adie concluded that the tonic convergence reaction in pupils apparently inactive to light is in all probability never a manifestation of syphilis of the nervous system and that the combination of this sign

with absence of tendon reflexes has never been observed in syphilis of the nervous system and is not one of its manifestations. He was not convinced that the syndrome may occur in cases of disseminated sclerosis (Strasburger) or of diabetes mellitus (Nonne) or after traumatism (Roemheld) or a stroke of lightning (W. Mayer). He stated the belief that the tonic convergence reaction is a disturbance sui generis and of unknown causation. With regard to incomplete forms of the syndrome he said:

> The diagnosis may still be made with some confidence if the eye signs are unilateral and the patient is young and free from other signs of organic nervous disease. A history of longstanding inequality of the pupils with recent sudden increase in size of the larger one, of wide variations in the size of the larger pupil, or the discovery of hippus confined to the larger pupil are important diagnostic points. . . . If persistent efforts to elicit tonic reactions have failed and a careful consideration of all the features of the case, age, sex, family and personal history, still leaves room for doubt, the appropriate tests to exclude syphilis must be made.

As to the nature of the syndrome, Adie expressed the opinion that it is of sympathetic origin, and he agreed with Behr, who placed the site of the disturbance of the pupils in the sympathetic part of the third nerve nucleus. Most persons who have made researches on Adie's syndrome have presupposed the sympathetic origin, but in 1940 Harold G. Scheie and Francis Heed Adler, who studied 11 patients with tonic pupils for their reaction to various drugs and who found marked sensitivity to a cholinergic drug, acetylbetamethylcholine (mecholyl), came to the hypothesis, like Axenfeld, Rothmann and others many years ago, that the site of the lesion is in the third nerve somewhere between the ciliary ganglion and the nerve endings in the sphincter muscle and that the lesion partially destroys these fibers.

In spite of the opinion of Adie, Behr, Foster Moore, Morgan and Symonds, Guillain and Sigwald and many other authors that pupillotonic reactions are never due to syphilis, a certain number of other authors, particularly French ones (for example Alajouanine and Morax, Harvier and Baudin, Laignel-Lavastine and Sittig and Saenger) emphasized that in a certain number of cases such reactions may be due to a syphilis, either congenital or acquired. Alajouanine and Morax made an especially important observation concerning a 20 year old woman with Adie's syndrome whose twin sister was suffering from bilateral syphilitic interstitial keratitis. All tests of the blood and the cerebrospinal fluid of both patients were negative. Alajouanine and Morax come to the conclusion that, while in a fairly large number of cases of pupillotonia there may be no evidence of a syphilitic origin, in other cases a syphilitic origin is either evident or probable. Syphilitically conditioned pupillotonia, according to these authors, is based either on congenital syphilis

or on an old syphilitic infection which has no strong tendencies to active progression and which therefore does not provoke any reactions in the blood or the cerebrospinal fluid. They stated the belief that the only difference between Argyll Robertson pupil and syphilitic pupillotonia lies in the fact that pupillotonia is based on a congenital or an old, attenuated syphilitic infection with little tendency toward further evolution.

PUPILLOGRAPHIC FEATURES

We may best consider the symptomatology by describing a few typical cases, in some of which there was and in some of which there was not a history of syphilis.

CASE 1.—A man, aged 26, who never felt ill but tired quickly, frequently suffered from headaches and was especially susceptible to infections, observed in the mirror an inequality of his pupils, and when he compared his eyes with those of his brothers and sisters he found that one brother and one sister showed the same phenomenon.[5] Both pupils were larger than average, the right pupil measuring 6.9 mm. and the left (the Adie pupil) 6.6 mm. in diameter. The right pupil apparently reacted well. As soon as a light stimulus was applied to either the right (reactive) or the left (rigid) pupil the right pupil contracted, but did not return to its original size, and became smaller than the rigid pupil.

Adie described the rigid pupil as generally the larger one; it dilates when in darkness for nearly an hour and when the patient comes out under bright light contracts sluggishly until it becomes smaller than it was before and even smaller than the other pupil. Our patient had been adapted for twelve minutes to darkness, and as the non-Adie pupil dilated faster than the Adie pupil, the former became larger than the latter (chart 1). But this dilation was immediately reversed when the non-Adie pupil contracted under the influence of a light stimulus.

In this case the Adie pupil did not react to light either directly or indirectly. In the case illustrated by chart 4 (the patient was a woman aged 22 with no tendon reflexes in the lower extremities), however, the larger pupil (the Adie pupil) had a small reaction to light both directly and indirectly. This reaction, which amounted only to 0.3 mm., had the long latency period of 0.4 second (the normal latency period is 0.3 second or less), and even the small contraction was sluggish.

The Non-Adie Pupil vs. the Adie Pupil.—The non-Adie pupil (that is, the left one in chart 4) is generally considered normal. It is true that it reacts both directly and indirectly and that the extent of the reaction is not diminished. But on repeated stimulation the non-

5. A similar case was observed and analyzed in collaboration with Professor Amsler, Lausanne, Switzerland. Twin brothers and a sister had Adie's syndrome, and their mother showed a tendency to pupillotonic reactions. Additional cases of this syndrome will be published later in collaboration with Dr. Amsler.

Adie pupil is sometimes found to fatigue more rapidly under indirect than under direct stimulation, as shown in chart 4, second line, where the fourth reaction of the non-Adie pupil amounts to 25 per cent less than the corresponding reaction on the first line. Neither does the so-called healthy pupil react quite normally. The latency period both for contraction and for dilation is prolonged, the contraction itself being prompt. This form of reaction, which is particularly typical in the case illustrated by chart 4, is a so-called tonohaptic reaction.

Dilation to Sensory and Psychologic Stimuli: The dilation to psychic or sensory stimuli exists in the Adie pupil but is relatively feeble and generally does not exceed 0.5 mm. On the other hand, the responses

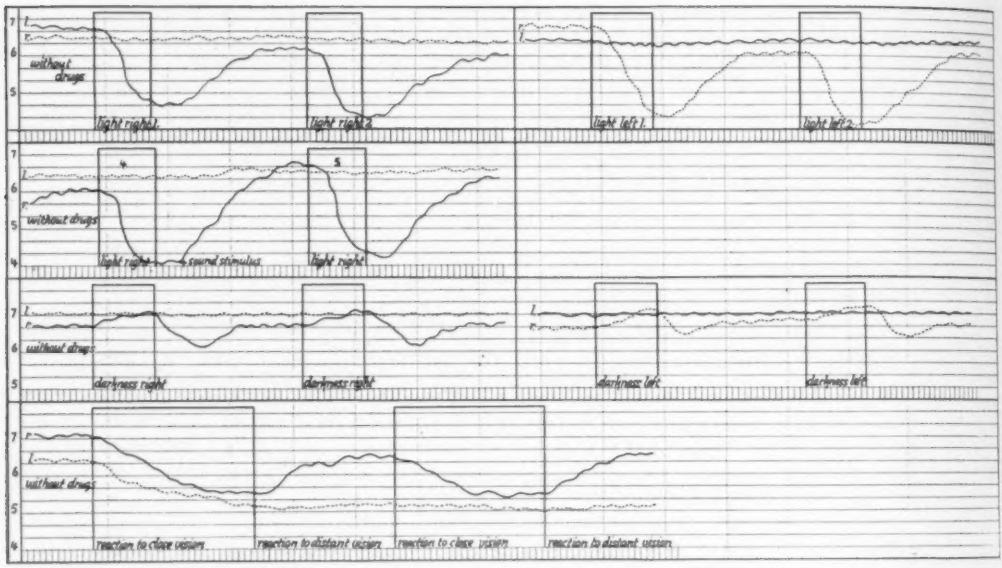

Chart 1 (case 1).—Pupillographic recordings of the Adie syndrome in a man aged 26 whose left pupil was immobile to light stimuli.

First line, two light stimulations of the right pupil (the latency periods of the [direct] contraction are long, and there are redilation and absence of consensual reaction) and two light stimulations of the left pupil (the direct reaction is absent and the consensual reaction present).

Second line, fourth and fifth light stimulations of the right pupil, with sound stimulation in the interval of darkness between the light stimulations. Both pupils dilate, the right more than the left (the psychosensory restitution phenomenon is present on the right and absent on the left side).

Third line, reactions to darkness without drugs; two darkness stimulations of the right pupil (a direct but no indirect reaction is present) and two darkness stimulations of the left pupil (no direct but a good indirect reaction is present).

Fourth line, reaction to near and to far vision. The Adie pupil contracts to near vision and does not dilate to distant vision.

are strong and generally even exaggerated in the non-Adie pupil, amounting sometimes to 2 or 3 mm.

Psychosensory Restitution Phenomenon: This phenomenon is absent in the Adie pupil; that is to say, the complete or partial absence of a response to light stimuli is not altered by sensory or psychologic stimuli. It is, however, exaggerated in the non-Adie pupil and more so after indirect than after direct stimulation; that is to say, the light reflex which was fatigued by a certain number of stimuli (as evidenced by a decrease in amplitude but an increase in the length of the latency period both for contraction and for redilation) becomes even more prompt, more

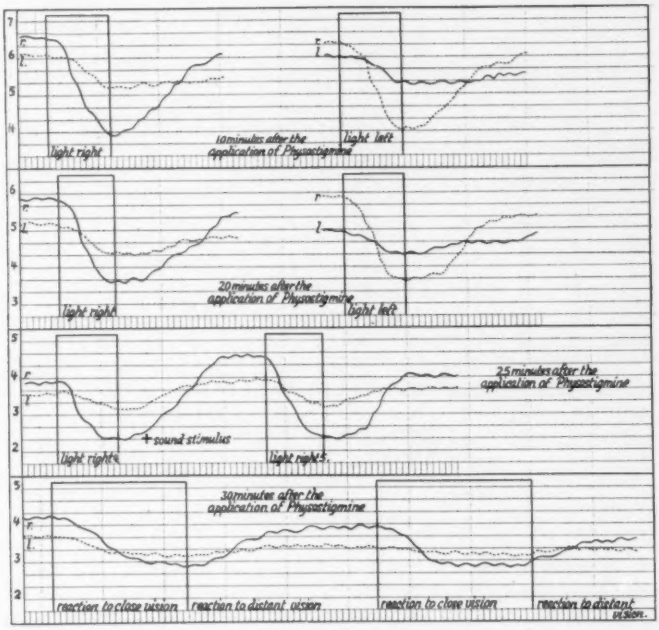

Chart 2.—Reactions after local application of physostigmine in the same case as that represented in chart 1.

First line, reactions to light ten minutes after the local application of physostigmine. The left (Adie) pupil is smaller and contracts to light, but redilates only after a long latency period.

Second line, reactions to light after twenty minutes. The left (Adie) pupil is still smaller and contracts to light, and redilation is better than after twelve minutes.

Third line, reactions to light after twenty-five minutes. Both pupils are smaller, the contraction to light on both sides is smaller than before, both pupils dilate to sound stimuli and the psychosensory restitution phenomenon is present on both sides.

Fourth line, reactions to near and to far vision thirty minutes after the application of physostigmine. Both pupils are small, and the Adie pupil is smaller than the non-Adie pupil and shows a tendency to react to distant vision, tiring quickly.

extensive and shorter as to latency period both for contraction and for dilation than it was on the occasion of its first reaction. It is, however, not larger than it was before the first light stimulus was applied. This is evident in the second line of chart 4.

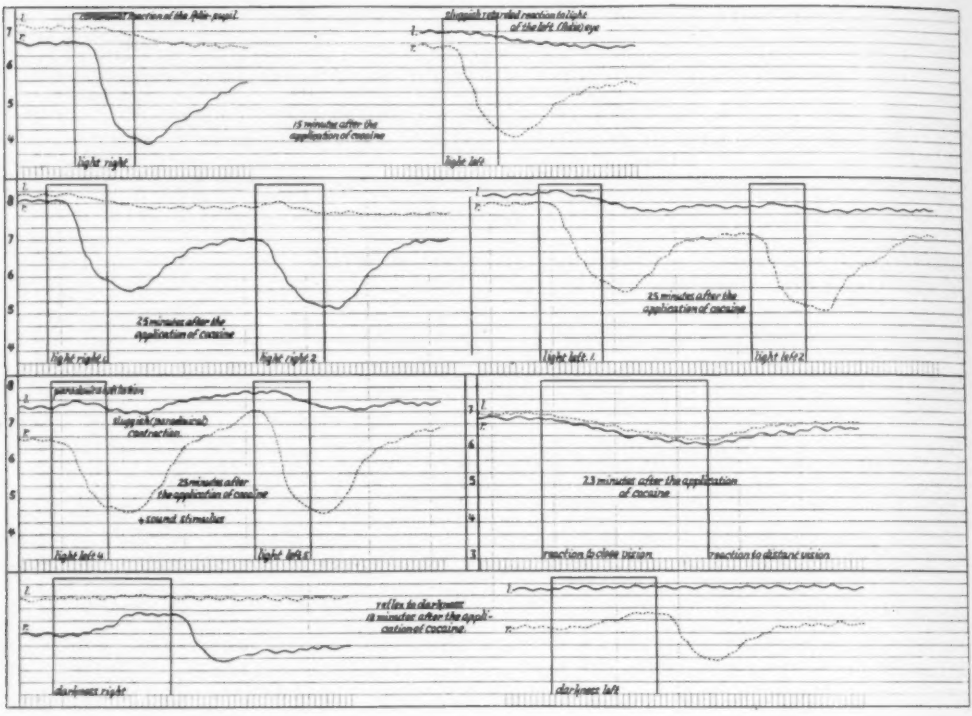
consensual reaction of the Adie pupil.
sluggish retarded reaction to light of the left (Adie) eye
15 minutes after the application of cocaine
light right
light left
2.5 minutes after the application of cocaine
light right 1
light right 2
light left 1
light left 2
paradoxical dilation
sluggish (paradoxical) contraction
25 minutes after the application of cocaine
a sound stimulus
light left 4
light left 5
23 minutes after the application of cocaine
reaction to close vision
reaction to distance vision
reflex to darkness 18 minutes after the application of cocaine
darkness right
darkness left

Chart 3.—Reactions after the local application of cocaine in the same case as that represented in charts 1 and 2.

First line, reactions to light after fifteen minutes. The contraction of the Adie pupil both to direct and to consensual stimulation is sluggish, the latency period is long and redilation is absent.

Second line, reactions to light after twenty-five minutes. The contraction of the Adie pupil to light both direct (0.6 mm.) and indirect (0.45 mm.) is sluggish and incomplete, the latency periods are long and there is initial dilation preceding contraction.

Third line, reactions to light after twenty-five minutes; fourth and fifth light stimulations of the left (Adie) pupil (the fourth stimulation is followed by "paradoxic" dilation) with a sound stimulation in the interval between them. Light stimulation is followed by a sluggish dilation of the left and by a prompt dilation of the right pupil, and the psychosensory restitution phenomenon is present on both sides.

Fourth line, reactions to darkness eighteen minutes after the application of cocaine. With stimulation of the right pupil the direct reflex is exaggerated, but the latency period is prolonged, and there is no indirect reflex. With stimulation of the left pupil there is no direct reflex, an indirect reflex is present and there is no prolongation of the latency period.

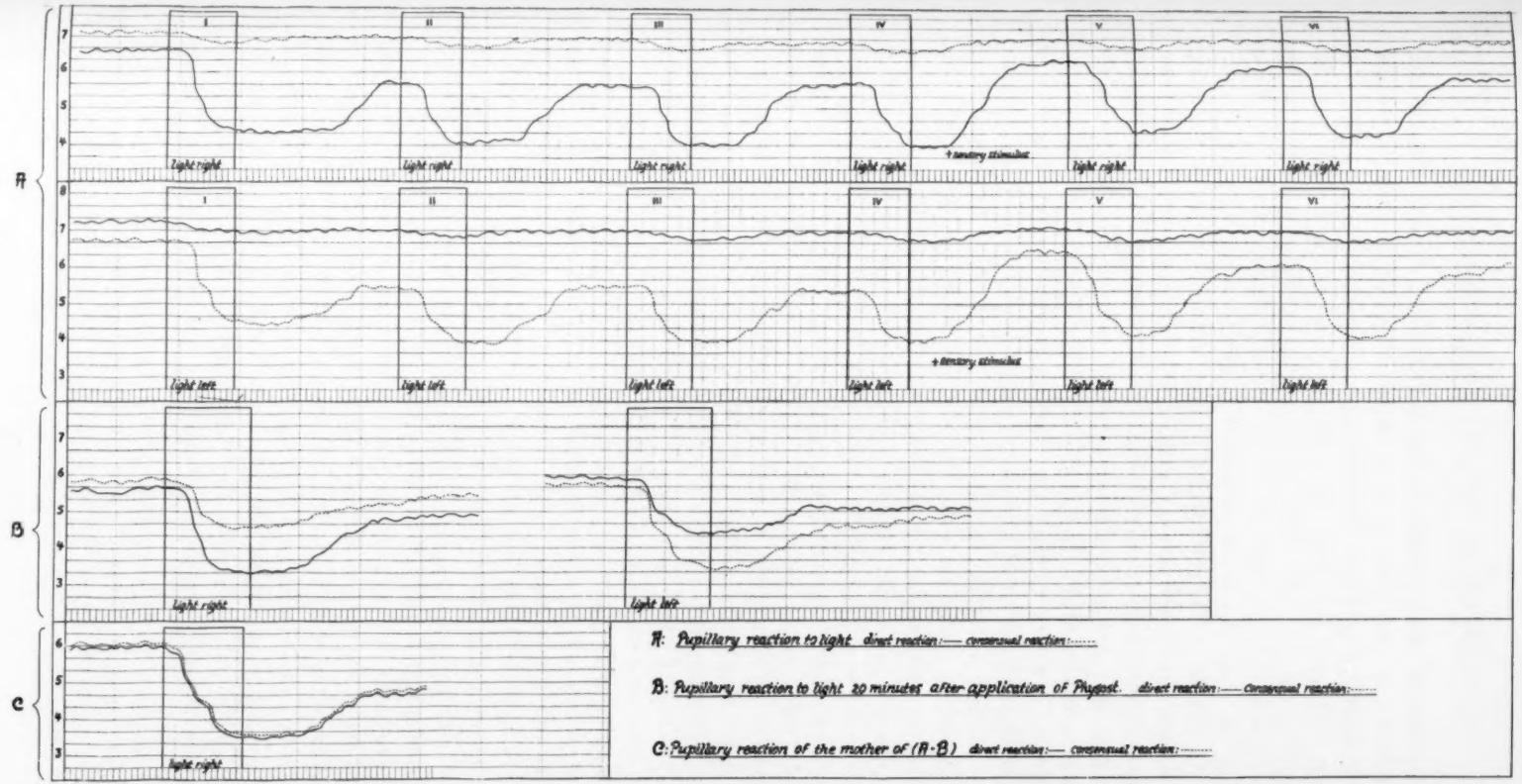

Chart 4.—Pupillographic recordings of the Adie syndrome in a woman aged 22. The left (Adie) pupil is not immobile to light; the right pupil shows tonohaptic reactions. *A*, six light stimulations of the right (first line) and the left (second line) pupil. Sensory stimulation (sound) after the fourth reaction elicits dilation of both pupils; the psychosensory restitution phenomenon is present only in the right pupil. *B*, pupillary reaction to light of both pupils twenty minutes after local application of physostigmine. *C*, light reaction (neurotonic) of the patient's mother.

Reaction to Near and to Distant Vision: Adie himself has emphasized that the reflex to near vision is especially characteristic; it may be observed in chart 1, fourth line. As in all typical cases it is sluggish and less extensive than in the healthy pupil. A peculiar characteristic of the Adie pupil is its failure to dilate on distant vision within an appropriate lapse of time. In some cases, particularly those in which the Adie pupil was originally larger than the so-called healthy pupil, the extent of the contraction to near vision is larger in the Adie-pupil, which therefore becomes smaller than the so-called normal one.

The redilation may require seconds or even minutes. It is a sluggish, uniform process and not a dilation by steps. The latency period for the contraction, too, is generally longer for the Adie pupil than for the non-Adie pupil; in order to elicit the reaction to near vision, therefore, it is frequently necessary that the patient maintain an energetic convergence attitude during a certain length of time, for instance for a period of from several to thirty seconds. It is characteristic of the pupillotonic convergence reaction that the mydriatic pupil reverts to miosis.

Pupillary Unrest and Hippus: The spontaneous movements of the iris border known as pupillary unrest exist both in the Adie pupil and in the so-called healthy pupil; they may be seen both in chart 1 and in chart 4 (they appear more active in the former) but do not appear exaggerated in either. It is known from Westphal and Lowenstein's researches [6] that different types of pupillary unrest appear in normal persons and that these types bear a direct relation to the types of light reflex. We could find no difference in the degree of pupillary unrest in the Adie and in the non-Adie pupil.

We agree with other observers that the size of the Adie pupil is not at all constant, but we could not find the phenomenon of hippus in our cases, as did Behr, Markus and Dressler. (We understand the term hippus to mean rhythmic but irregular oscillations of the pupil occurring within seconds, amounting to several millimeters and being independent of light, convergence or sensory and psychologic stimuli.) Deformities in the shape of the pupil, however, could frequently be observed.

Reactions to Drugs: Adie emphasized that the reactions of the tonic pupil to drugs are not modified, that the pupil dilates well in response to mydriatics and contracts with physostigmine. Most later observers confirmed Adie's observations and found the reactions to drugs to be normal. Barré and Klein infiltrated the inferior cervical ganglion with procaine hydrochloride and found that the Adie pupil became extremely large: the reflex to light remained absent but the reflex to near vision

6. Lowenstein, O., and Westphal, A.: Experimentelle und klinische Studien zur Physiologie und Pathologie der Pupillenbewegungen mit besonderer Berücksichtigung der Schizophrenie, Berlin, S. Karger, 1933.

reappeared for several minutes. Alajouanine and Morax, however, could not confirm this observation.

Werner Kyrieleis indicated that under the influence of 0.0005 to 0.0002 Gm. of strychnine sulfate subcutaneously injected the reactivity to light of the Adie pupil returned in a certain number of cases, but this observation could not be confirmed by Alajouanine and Morax, who saw no modification of the light reflex after the injection of strychnine.

In 1938 one of us [7] found that in a certain number of cases of pupillotonia the reaction to light returned and the reaction to near and

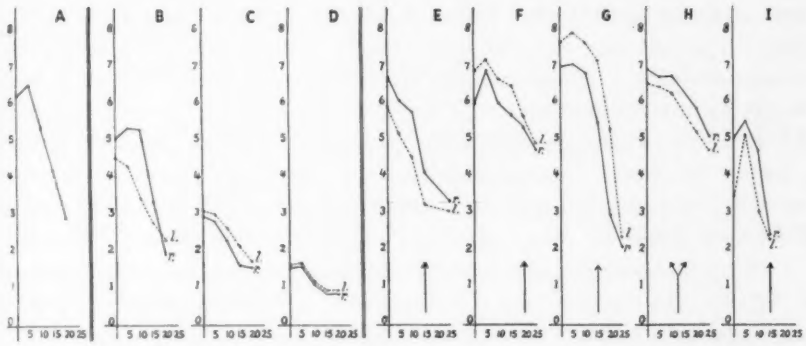

Chart 5.—The contractile effect of physostigmine on the pupillary diameter. *A*, normal eye: The contraction is preceded by a short preliminary stage of dilation. *B*, a case of neurosyphilis: The left pupil is immobile to light and to near and to distant vision, and the right pupil reacts to light and to near vision; physostigmine suppresses the reaction to near vision. *C*, case of neurosyphilis: The Argyll Robertson phenomenon is present on both sides; physostigmine is without effect on the light reflex but diminishes the reaction to near vision. *D*, case of neurosyphilis: There is nearly complete immobility of both pupils; physostigmine is nearly without effect. *E*, case of the Adie syndrome: Physostigmine contracts the pupil but restores its ability to react to light; the maximum of the light reaction occurs after fifteen minutes (see arrow). *F*, case of the Adie syndrome: The maximum of the light reaction occurs after twenty minutes (see arrow). *G*, case of the Adie syndrome: The maximum of the light reaction occurs after fifteen minutes (see arrow). *H*, case of the Adie syndrome: The maximum of the light reaction occurs after ten to fifteen minutes (see arrow). *I*, case of the Adie syndrome: The maximum of the light reaction occurs after fifteen minutes (see arrow).

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7. Lowenstein, O.: L'épreuve à éserine; son importance pour le diagnostic différentiel entre les troubles syphilitiques du système nerveux central et le syndrome d'Adie, Schweiz med. Wchnschr. **20**:377, 1939; Réunion de la Société de neurologie de Paris, April 28, 1938; Société de'ophtalmologie de Bruxelles, Nov. 26, 1938; Société ophtalmologique du Léman à Genève, Dec. 10, 1938. Les troubles du réflexe pupillaire à la lumière dans les affections syphilitiques du système nerveux central, Paris, Gaston Doin & Cie, 1939, p. 16.

to distant vision lost its tonic character after the instillation of physostigmine into the conjunctival sac. One drop of 0.3 per cent solution of physostigmine salicylate was instilled into each sac; five minutes later a second drop and after another five minutes a third drop were instilled. Both the Adie and the non-Adie pupil contracted (chart 5). At the maximum of the contraction, which followed a short stage of initial dilation, the pupils were more nearly equal than before. The beginning of the contraction occurred simultaneously in the two eyes; in other words, the sensitivity to physostigmine was the same for the two pupils, (as emphasized by David Cogan), at any rate for the concentration (0.3 per cent) in which the physostigmine was instilled. A light stimulus applied after fifteen to twenty minutes was able to elicit a reaction in the now smaller Adie pupil. Of 10 cases, we found the maximum reaction fifteen minutes after instillation of the first drop in 6, twelve to fifteen minutes after in 2 and fifteen to twenty minutes after in 2. In cases of neurosyphilis also we found a contraction with physostigmine but never a reappearance of the capacity of the pupil to react to light; nor did we find this capacity in cases of syphilitic Argyll Robertson pupil or in cases of syphilitically conditioned pupillotonia.

Chart 6 shows the modification of the Adie pupil by physostigmine in 3 cases. In the first case the Adie pupil, with a diameter of 7.1 mm., had regained its ability to contract directly and indirectly to light, after physostigmine had contracted it to 5.9 mm. (first line, chart 6). In the second case, the 6.1 mm. Adie pupil had to contract to 3.2 mm., and in the third case (third line) the 7.1 mm. Adie pupil had to contract to 5.5 mm. in order to regain the capacity of reacting to light. These 3 cases show that the degree to which the capacity of reacting to light is regained may be high or low; in them it varied from 60 to 30 per cent of the capacity of the so-called normal pupil (first and third lines, chart 6).

The reaction of the Adie pupil to cocaine was also normal, consisting of a short initial contraction followed by a strong dilation. Under the influence of cocaine, small sluggish atypical reactions to light could be elicited. The reaction, however, did not cease when the light stimulus came to an end but continued even in darkness, as may be seen in chart 3. There was sometimes even a so-called paradoxic dilation to light about twenty-five minutes after the first drop of cocaine (1 per cent cocaine hydrochloride) was instilled. The reaction to sensory stimuli (dilation) was improved both by cocaine and by physostigmine (charts 1, 2 and 3).

The capacity of the Adie pupil to react to light to a low degree and in an abnormal and sometimes paradoxic manner under the influence of

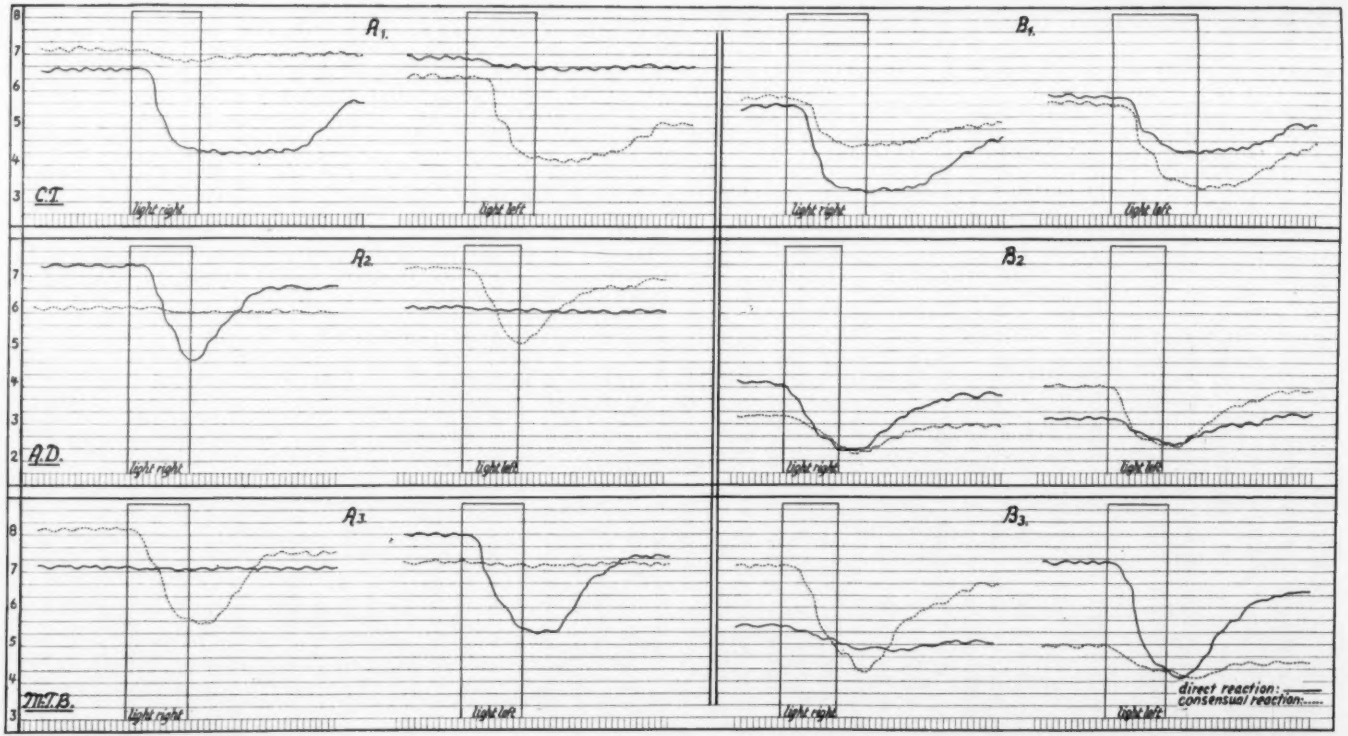

Chart 6.—Modification of the light reflex by physostigmine in 3 cases of the Adie syndrome. A_1 A_2 and A_3, the light reflex without application of drugs. B_1 B_2 and B_3, the light reflex after local application of physostigmine. Note that the degree to which the capacity of reacting to light is regained varies greatly in these cases.

cocaine was observed in cases of Adie's syndrome not syphilitically conditioned, in cases of syphilitically conditioned pupillotonia and in cases of Argyll Robertson phenomena. The capacity to regain the light reaction and to improve the pupillotonic reaction to convergence under the influence of physostigmine could be observed in our material only in cases of a nonsyphilitically conditioned Adie syndrome.

SYPHILITIC PUPILLOTONIA AND ARGYLL ROBERTSON'S PHENOMENON: REPORT OF CASES

CASE 2.—A woman 61 years of age had typical pupillotonia (chart 7). The tonic pupil was the larger one but became the smaller one immediately after the first light stimulus struck the eye. It reacted to light to the extent of about 0.3 mm.; that is to say, it was practically immobile. The nontonic pupil reacted to light both directly and indirectly. The dilation to sensory stimuli was more extensive than in the non-Adie pupil. The Piltz-Westphal phenomenon was absent in the tonic pupil. The reaction to near and to distant vision is to be seen in chart 7 *A*.

Physostigmine provoked a contraction of both pupils but did not increase the light reaction of the tonic pupil. Cocaine dilated the pupil and did not provoke a restitution of the light reaction.

The patient had been married from 1901 to 1903 to a man who later died of dementia paralytica. There had been no pregnancy. Since 1904 she had suffered from severe headaches, which frequently disturbed her sleep. In 1904 a neurologic examination gave negative results, and the Wassermann reaction in 1909 was negative. At the time of our examination the right pupil was larger than the left. The right knee jerk was more active than the left. The Babinski reflex was elicited on both sides, being more typical on the right side. The Oppenheim sign was present on the left side. The adductor reflexes were unequal and crossed from the two sides. The tonus of the left lower extremity was increased. The Wassermann reaction of the blood and of the spinal fluid were negative. All other tests of the spinal fluid gave negative results.

Antisyphilitic treatment resulted in a remarkable improvement of the spastic symptoms in the lower extremities. The diagnosis was syphilis cerebri.

CASE 3.—A woman 45 years old who had contracted syphilis fifteen years before had typical tabes dorsalis with absence of deep reflexes, ataxia, sensory disturbances, hypotonia of the legs and arthropathy of the hip joint. The pupils were unequal and large, the diameter of the right being 6.3 mm. and that of the left being 6 mm.

The right pupil was immobile to light and reacted to near vision. It was also immobile to sensory stimuli. The left pupil reacted to light (both directly and indirectly), to sensory stimuli and to distant and near vision. Under the influence of physostigmine both pupils became smaller, the left being more sensitive to physostigmine than the right (chart 8).

It may be seen from chart 8 that at no moment of the physostigmine contraction did the pupil react to light. On the other hand, the reaction to near and to distant vision, present before the application of physostigmine, had completely disappeared twenty-five minutes after the application of physostigmine, and there was even a tendency toward a paradoxic dilation on close vision.

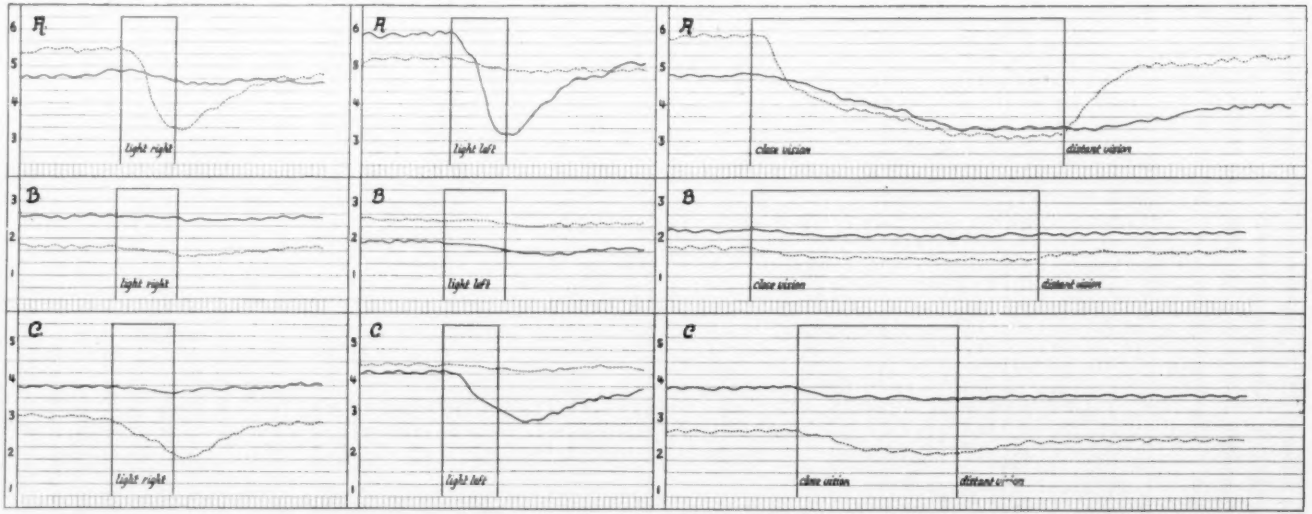

Chart 7 (case 2).—Pupillographic recordings of syphilitic pupillotomia in a woman 61 years of age. *A:* first section, light reaction after stimulation of the right pupil (the direct reflex is practically absent, and the consensual reflex is present); second section, light reaction after stimulation of the left pupil (the direct reflex is present, and the consensual reflex is feeble); third section, reaction to near and to distant vision (there is a tonic reaction of the right pupil). *B,* the physostigmine test: Physostigmine provokes a contraction of both pupils; it does not increase the light reaction of the tonic pupil, and it does decrease the light reflex of the nontonic pupil; the reflex to near and that to distant vision are greatly decreased. *C,* cocaine test: Cocaine dilates the pupils and does not cause a restitution of the light reaction.

Case 4.—The patient, a woman aged 38, had dementia paralytica with small pupils and a—clinically—typical Argyll Robertson phenomenon. The reaction to light was nearly absent on both sides (chart 9), amounting to 0.33 mm. on the left and 0.23 mm. on the right. The reaction to near vision was 1 mm. on each

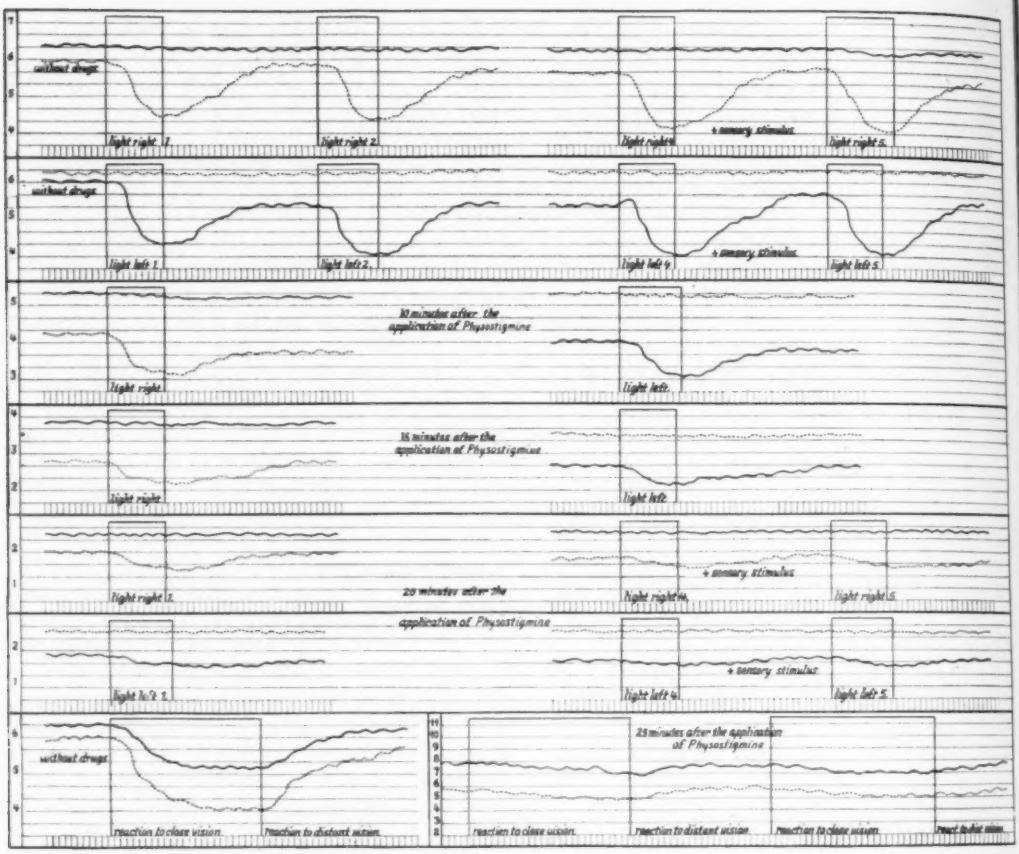

Chart 8 (case 3).—Pupillographic recordings of a woman 45 years of age with tabes dorsalis; the pupils were unequal and large. In the first six lines the unbroken line shows the direct reaction and the broken line the consensual reaction. First line, light stimulation of the right pupil. The direct reaction is absent, and the consensual reaction is present. The right pupil does not react to sensory stimuli, but a feeble psychosensory restitution phenomenon is present. Second line, light stimulation of the left pupil. The direct reaction is present, and the consensual reaction is absent. The light reflex is quickly fatigued (note the initial dilation of the fourth reaction). The psychosensory restitution phenomenon and dilation to sensory stimuli are present. Third to sixth lines, inclusive, physostigmine test. The drug causes a contraction of both pupils and does not restore the ability to contract to light. Seventh line (unbroken line, right eye; broken line, left eye) reaction to near and to distant vision. Physostigmine diminishes the reaction to near vision.

side. The pupillary diameter amounted to 4.3 mm. on the right and 4.2 mm. on the left side. Under the influence of cocaine the light reflexes improved after ten minutes (fourth line, chart 9), and after fifteen minutes the improvement remained in the right pupil but had disappeared in the left.

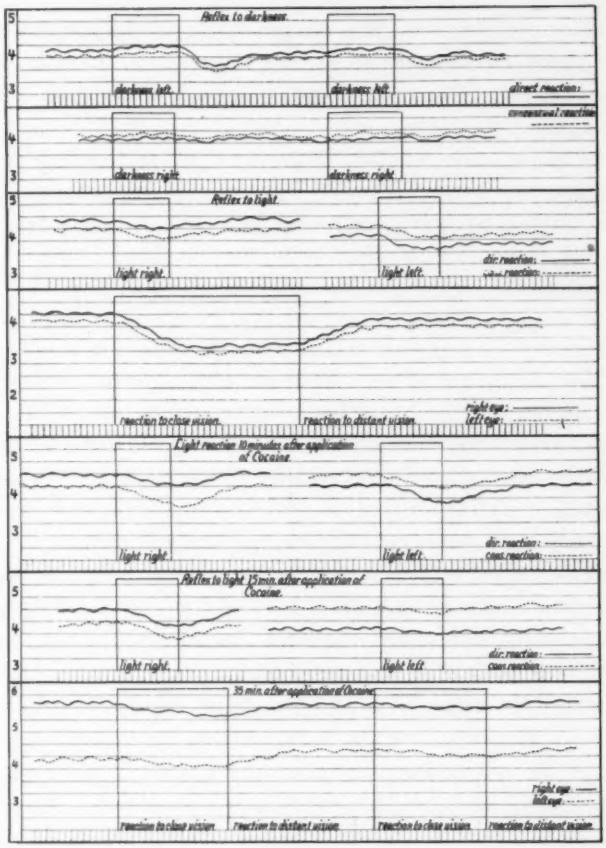

Chart 9 (case 4).—Pupillographic recordings for a woman aged 38 with dementia paralytica, small pupils and a—clinically—typical Argyll Robertson phenomenon. First line, reflex to darkness of the left pupil: The direct and the consensual reaction are feeble though present both in the primary and in the secondary part. Second line, reflex to darkness of the right pupil: The direct and the consensual reaction in both parts are practically absent. Third line, reflex to light: This is feeble, practically absent, on both sides (0.3 mm. on the left side and 0.2 mm. on the right). Fourth line, reaction to near and to far vision. Fifth line, cocaine test: Ten minutes after local application of cocaine hydrochloride the light reflexes have improved. Sixth line, fifteen minutes after local application of cocaine: The improvement persists in the right pupil but has disappeared in the left. Seventh line, reaction to near and to far vision thirty-five minutes after local application of cocaine. The reflex has decreased.

These cases show what we have already stated, that under the influence of physostigmine the Adie pupil reacts not only to light but to distant vision. Ten minutes or more after the application of physostigmine the Adie pupil reacts directly and consensually to light. The induced reactivity reaches a maximum in about fifteen to twenty minutes. The degree of the reactivity is a characteristic of the individual patient. In typical cases the magnitude of the induced contraction to light is nearly one-half that of the normal pupil. Both contraction and dilation remain sluggish.

Occasionally cocaine is found to have a restorative effect on the light reaction of the Adie pupil. Ten to fifteen minutes after the instillation of cocaine the pupil is immobile, or nearly immobile, for the duration of the light stimulus, but after the light stimulus has been removed it slowly begins to contract. This paradoxic contraction during the period of darkness is of long duration (chart 3), is sluggish and is followed by a comparatively sluggish dilation; sometimes after application of cocaine there is a paradoxic dilation to the light stimulus. This behavior may be observed with both direct and consensual light, but in all cases the contraction is small when compared with that of the healthy pupil. Under the influence of cocaine the dilation reflex to sensory stimuli appears slightly increased and sometimes (chart 3) the convergence reaction is restored after twenty-five minutes.

In cases of syphilitic origin, however, physostigmine diminishes the size of the pupil without restoring the light reaction. Moreover, this drug rather rapidly diminishes the light reaction on the unaffected side. The convergence reaction is not restored.

By contrast, in cases of syphilitic origin just as in cases of Adie pupillotonia, a restoration of the light reaction by cocaine ten to fifteen minutes after its application is occasionally observed. Yet the restored function is limited, and the reaction to near vision is not restored. The restoration of function in syphilitic pupils is quantitively identical with the capacity for psychosensory restitution.

In correlating the differences between the Adie syndrome and syphilitic pupillary symptoms it must be noted that pupillotonic factors characterizing the Adie syndrome in most cases readily facilitate a differential diagnosis. In cases, however, in which the syphilitic symptoms nearly parallel the Adie symptoms, a differentiation can be made by means of physostigmine. For, whereas physostigmine contracts the Adie pupil as well as the syphilitic pupil, the Adie pupil in contrast to the syphilitic pupil regains its capacity to contract to light as well as to dilate to distant vision. On the other hand, the effect of cocaine is not specific in the Adie pupil.

Among our 14 cases of pupillotonia, there were 3 which proved to be of syphilitic causation. The 3 patients were over 40 years of age and had acquired syphilis many years previously, and the infection was relatively benign. These circumstances agree with those described in the literature (Alajouanine and Morax), in which the benign character of the syphilitic infection underlying syphilitic Adie pupil is emphasized. Our other patients were young, with no evidence to support a supposition of congenital syphilis. Therefore we are not able to decide whether or not in cases of Adie pupil occurring in persons with congenital syphilis the reaction to physostigmine will be positive. Such cases as those described by Alajouanine and Morax, in which one twin sister had interstitial syphilitic keratitis and the other the Adie syndrome, would enable us to decide whether or not one can distinguish with the physostigmine test cases in which the cause is due to congenital syphilis and cases of heredodegenerative conditions. We were not fortunate enough to find such cases.

CAUSE: SYPHILIS OR HEREDODEGENERATION?

Among 14 cases we found 3 in which a syphilitic genesis could be postulated. We have already emphasized that in these cases the Adie pupil was the result of a relatively benign infection. There is doubt, therefore, that pupillotonia as such may be caused by syphilis and if combined with tabetic symptoms may simulate a true Adie syndrome.

There have been reported a certain number of cases (e. g. by Saenger, Sittig, Chavanny, Alajouanine and Morax) in which the Adie syndrome was related to congenital syphilis; the relation was made evident by the fact that the parents or grandparents had shown evidence of syphilitic infection. There is, however, only 1 case in which the circumstances were really convincing, that described by Alajouanine and Morax, and already mentioned, of the twin whose Wassermann reaction of the blood was positive but whose cerebrospinal fluid reactions were negative. We do not at all wish to deny the possibility that congenital syphilis may be the cause of Adie symptoms, but we are not able to confirm it positively. Only one fact resulting from our pupillographic studies tends to support the hypothesis of Alajouanine and Morax: Generally, syphilitic lesions of the central nervous system provoking pupillary symptoms concern the parasympathetic path of pupillary control. In cases of congenital syphilitic lesions of the central nervous system, however, participation of this path is extremely frequent, taking the form particularly of anisocoria. We shall show later that we were seeking the site of the Adie lesion in the sympathetic centers of pupillary control.

As we sought in vain for evidence of congenital syphilitic etiologic factors, we made pupillographic studies of the parents of our patients. We were able to examine seven mothers (unfortunately, no fathers), and in no less than four we could detect modifications of the pupillary reflexes. In chart 8 may be found represented two types of these. In both there were tonic reactions to light but with convergence the reactions were intact. The light reaction was what is generally called neurotonic, which means that the contraction is intact but that the contracted pupil does not redilate or does so only after a long latency period when the light stimulus is removed. In order to make clear this neurotonic character we show (charts 10 and 11) two reactions in each subject in whom the light stimulus did not take more than 0.25 second. (That is

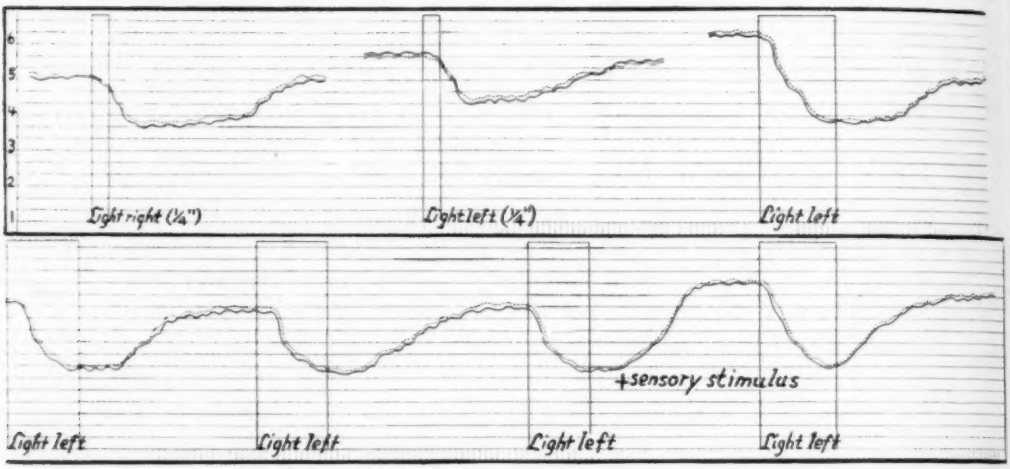

Chart 10.—Neurotonic pupillary reaction to light of the mother of a patient with the Adie syndrome. In charts 10 and 11 the unbroken line represents the direct reaction and the broken line the consensual reaction.

to say, the light stimulus was removed just after the pupil had begun to react.) We got not only a full contraction ("all or nothing law") but even a well developed neurotonic reaction—better developed in the case illustrated by chart 11 than in that illustrated by chart 10.

Both cases are highly interesting. Neither mother knew anything of her pupillary anomalies, but, interestingly enough, both showed a psychopathic constitution, just as did the daughters.[7a] The mother whose

7a. Kennedy and associates (Kennedy, F.; Wortis, H.; Richard, T. D., and Fair, B. B.: Adie's Syndrome, Arch. Ophth. **19**:68-80 [Jan.] 1938) drew attention to the evidence of emotional disturbances in patients with Adie's syndrome.

pupillary reactions are illustrated in chart 11 manifested a distinct anisocoria of both static and dynamic nature, which directed our attention to localization in the sympathetic part of the autonomic system. Common to both mothers was a great exaggeration of the psychosensory restitution phenomenon, which was even able to suppress for a short time the tonic character of the light reaction. However, the phenomenon lasted but a short time and was concomitant with an increased fatigability of the pupillary reflexes. These and other cases show a genetic relationship between pupillotonia in the sense of Adie and what we have always distinguished as neurotonia.

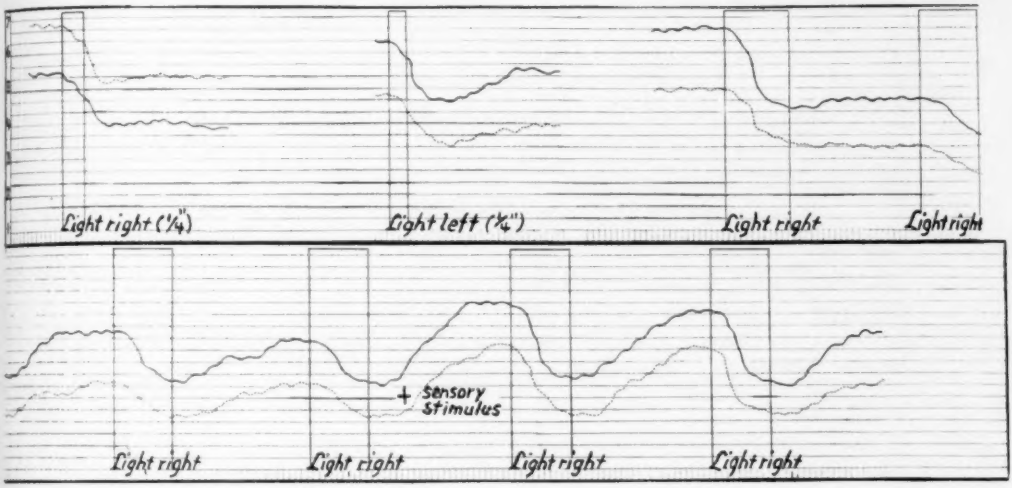

Chart 11.—Neurotonic pupillary reaction to light of the mother of a patient with the Adie syndrome.

NEUROTONIC REACTIONS

In 1914 Piltz described a pupillary reaction characterized by a good contraction to light which does not increase with a further influx of light. Piltz saw this reaction in a case of psychosis and Westphal had seen it in 1913 in a case of neurosis. Behr described 2 other cases in 1924, the first of "syringomyelia" and the second of encephalitis lethargica. The reaction to convergence as well as the reaction to sensory stimuli was present. After the patient had been in darkness for several minutes the pupils became large and reacted well to artificial light, but they remained inactive on exposure to daylight. Behr, Bing and Franceschetti emphasized the extreme rarity of this symptom, which according to Bing and Franceschetti is a form of pupillary sluggishness which occurs particularly in dementia paralytica. According to Behr

it is perhaps a central sympathetic disturbance, but he has said that a systematic classification is impossible at present.

Such reactions are considered extremely rare, and we could find only 4 cases in the literature. On the other hand, pupillography discloses neurotonic symptoms as being quite frequent. They are illustrated by the following case:

CASE 5.—A woman aged 45 was seriously psychopathic, with a tendency to reactive depressions. Her parents (first cousins) were both suffering from depressions. Nothing was known of a syphilitic infection in either the patient or her parents. She had been suffering from insomnia for a long time; she was highly excited at night, moving from side to side and sleeping only three or four hours. She was dissatisfied with herself, her life and her surroundings, tired quickly and was asthenic in all her reactions. The neurologic examination

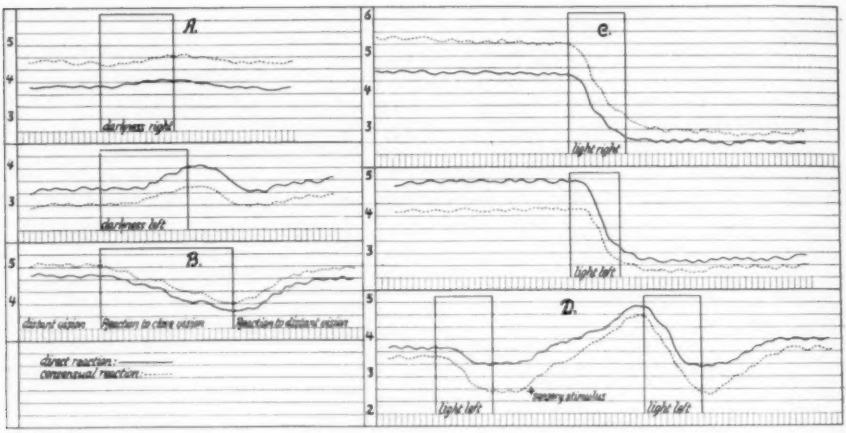

Chart 12 (case 5).—Pupillographic recordings of a woman 45 years of age with neurotonia and anisocoria. *A*: first line, reaction to darkness of the right pupil (second line) and of the left pupil (second line). *B*, reaction to near and to far vision. *C*, neurotonic reaction to light stimulation of the right pupil (first line) and of the left pupil (second line). *D*, the psychosensory restitution phenomenon is exaggerated, and there is strong dilation to sensory stimulation.

disclosed that the deep reflexes, especially the knee and the ankle jerks, were feeble and were obtained only by the Jendrassik maneuver. Dermographia was present, as was Romberg's sign; the movements of the eyes were intact, and there was no nystagmus.

Pupillographic studies were made with the patient wearing glasses, as spasms of accommodation occurred as soon as she tried to see without them.

Chart 12 shows strong anisocoria, the larger pupil having a diameter of 5.3 mm., and the smaller a diameter of 4.7 mm. The contraction to light (chart 12 *C*) was rapid and extensive, but redilation was absent. In contrast to the reaction to light, that to near and that to distant vision were good (chart 12 *B*). However, the darkness reflex was marked by a number of anomalies on the right side. There was no real dilation and no subsequent real contraction. The left pupil

reacted much better to darkness, but there was a distinct prolongation of the latency period, which was also evident in the secondary contraction, following the first dilation.

Physostigmine provoked a strong change, at the culmination of which the redilation following the first reaction to light seemed to be a little increased, whereas epinephrine and cocaine applied locally were without influence on the light reflex. In this respect there were certain similarities to Adie's syndrome, at least in tendencies. The dilation due to psychologic or to sensory stimuli was strong; the psychosensory restitution phenomenon was also strong and eliminated for a moment the tonic reaction. Pupillary unrest appeared rather exaggerated.

Thus it may be seen that the neurotonic phenomenon is related to pupillotonia, particularly to Adie's syndrome. The relation is on the basis of heredity, and many of the symptomatologic features are similar.

NATURE OF ADIE'S SYNDROME

The incorporation of pupillotonia as a clinical entity, especially in the form of Adie's syndrome, is extremely difficult. As long as there are no anatomic observations on which to base a theory, any opinion must necessarily be provisional and have limited value.

Adie agreed with Behr in the opinion that there must be a "peculiar disturbance of the function of the vegetative portion of the third nerve nucleus," and he found, that this notion receives some support from a consideration of the peculiar symptomless areflexia which occurs in a number of disorders of the vegetative nervous system, in dystrophia myotonica and in other myopathic atrophies, in which the knee and ankle jerks are often lost. Areflexia is also seen in myasthenia gravis, family periodic paralysis and other disorders in which the vegetative nervous system is involved. In contrast to Adie and Behr, Kyrieleis, basing his opinion on experiments with strychnine, sought the lesion in the relay system to the sphincter nucleus, and Scheie and Adler, basing their view on experiments with acetylbetamethylcholine, came to the conclusion that the site of the lesion is in the third nerve somewhere between the ciliary ganglion and the nerve endings in the sphincter muscle and that it partially destroys the postganglionic parasympathetic fibers of the muscle.

What is pupillography able to contribute to the problem? What facts have been elicited by it?

1. The non-Adie pupil in cases of the Adie syndrome does not react normally; its reaction is frequently of the so-called tonohaptic type.

2. Pupillotonic reactions form a hereditary unit with neurotonic reactions.

3. Physostigmine makes the Adie pupil react not only to light but to far vision. It is important to emphasize that the reactivity develops

toward a maximum while the pupil contracts under the influence of the drug. After the maximum of reactivity has been reached the drug continues to make the pupil contract while the reactivity to light and to far vision diminishes.

4. The pupillary unrest is not decreased but is perhaps increased in the Adie pupil. It is certainly increased in neurotonia.

The Adie pupil is not hypersensitive to physostigmine, at least not in 0.25 per cent concentration, as both pupils, the Adie and the non-Adie, contract in parallel fashion. On this point we wish to confirm Cogan's findings. It is known that physostigmine is not effective directly but as a catalyst activates the acetylcholine present. It is effective only if acetylcholine is present at the site of the effect; this effect therefore is supposed to be localized in the periphery, i. e. in the iris itself. The pupillary reflex to light and to distant vision reappears under the influence of physostigmine only during a certain period, not before the beginning of this period and not after its end, during which the effect becomes continuously stronger while the degree of reactivity, beginning at zero, increases continuously until it reaches a maximum and returns steadily to zero after having run through this maximum. In other words, the reactivity of the Adie pupil depends on the equilibrium between the amount of acetylcholine and the amount of epinephrine present at the site of the effect. If the effect of the acetylcholine present is continuously reenforced by the presence of physostigmine, an increasing amount of epinephrine is made ineffective and there must come a moment when the equilibrium is complete enough to allow the pupil to contract to light. If the activation of acetylcholine becomes too strong, this favorable equilibrium no longer exists.

We may assume that in pupillotonia the sympathetic periphery has lost its check and severe sympathetic irritation takes place. This preponderance of sympathetic control is due to a central sympathetic irritability provoking a spasm in the periphery.

On the other hand, we are not able to explain the fact that cocaine also produced a reactivation of the Adie pupil. But we must not forget that the reaction to light it produced never amounted to more than 0.6 mm., was highly atypical and very sluggish, with a latency period up to one second or more, and frequently occurred after the light stimulus had stopped. Repetition of the light stimulus generally provoked a paradoxic dilation. The Argyll Robertson pupil under the effect of cocaine regains its reaction to light up to a certain degree in a number of cases.

In these cases, like Behr we place the lesion in the system of intercalated ganglions located cephalad to the Westphal-Edinger nucleus. In cases of mydriasis we seek the lesion in the Westphal-Edinger nucleus itself; but in these cases there usually exists an absolute or incomplete

rigidity. When there is a complete absence of acetylcholine in a mydriatic pupil physostigmine neither produces contraction nor has any effect on the light reaction; one cannot expect a reaction to light to be produced by this drug when the quantity of acetylcholine liberated is no greater than the amount of epinephrine present. However, if, as is generally supposed, in cases of Argyll Robertson pupil a lesion in the intercalated ganglions located cephalad to the Westphal-Edinger nucleus provokes a constant stimulation of the nucleus and thereby causes the pupil to be small and immobile, conditions are somewhat similar (even though exhibiting the opposite feature) to those described for Adie's pupillotonia; in other words, cocaine will activate the epinephrine present and thereby bind a certain amount of acetylcholine, which is present in surplus, by the constant stimulation of the Westphal-Edinger nucleus. In the same way we are able to explain another fact, described by one of us,[8] who in a certain number of cases of syphilitically conditioned immobility of the pupil found that a sensory stimulus dilated the pupil and restored the reaction to light (psychosensory restitution phenomenon). There is some evidence for the supposition that the psychosensory restitution phenomenon is due to a liberation of epinephrine. If it is, the liberated epinephrine would bind the surplus of acetylcholine liberated by the constant irritation of Westphal-Edinger nucleus. In this way the pupil would recover an equilibrium which would enable it to contract to light.

We found that in cases of unilateral pupillotonia the non-Adie pupil shows a type of reaction called tonohaptic. Lowenstein and Westphal [6] described this reaction type in 1933, when they first found it in patients showing Westphal's changing catatonic pupillary rigidity. Later on they found it in cases of postencephalitic lesions, of dystrophia adiposogenitalis, of Simmonds' cachexia and of diabetes insipidus; Lowenstein and Franceschetti found it in cases of retinitis pigmentosa. We refer this type of pupillary reaction either to the great vegetative centers in the diencephalon or to the connections of the diencephalon to the adjacent parts of the mesencephalon. As a matter of fact, whoever sees Westphal's catatonic pupillary immobility (spasmus mobilis) feels that this phenomenon is similar and perhaps identical with pupillotonia. There is a great probability that Adie's syndrome might be localized in the same region.

In following up this theory, the fundamental point of which concerns disturbances of the sympathetic and parasympathetic equilibrium, we also find an explanation for the absence of redilation after contraction on near

8. Lowenstein, O.: Der psychische Restitutionseffekt: Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion, Basel, Benno Schwabe & Co., 1937, pp. 58-68.

vision. The consideration that the irritability to convergence is stronger than that to light is familiar and may be associated with the neurogenic theory of the reaction to convergence. The force of convergence is greater than that of the reaction to light and just sufficient to overcome the sympathetic innervation. The absence of redilation on distant vision must be explained as a reactive spasm of the sphincter iridis muscle which replaces the spasm of the dilator muscle—a phenomenon analogous to that observed in cases of postencephalitic involvement, particularly in the muscles of the extremities.

The phenomena of neurotonia may be explained in a similar way: We would postulate a lesion of similar localization but of irritative supranuclear rather than of nuclear character. As the psychosensory restitution phenomenon is able to abolish the neurotonic character of the reaction, we have to assume that the liberation of epinephrine adds what is lacking; that is to say, we are dealing with a sympathetic deficiency.

Kyrieleis' supposition that Adie's syndrome must be localized in the intercalated ganglions cephalad to the Westphal-Edinger nucleus cannot be confirmed. Such a localization would lead to a small Argyll Robertson pupil but not to a large tonic one (Behr).

We have mentioned Adler and Scheie's theory according to which Adie's syndrome is due to a peripheral nerve lesion somewhere between the ciliary ganglion and the nerve endings in the sphincter muscle with partial destruction of certain nerve fibers. They found pupillotonia in 2 cases of ablatio retinae; in these cases, too, a hypersensitivity to a cholinergic substance (mecholyl) developed, and they stated the belief that this was due to damage done to the long ciliary nerves. David Cogan could not confirm the existence of hypersensitivity to cholinergic substances in cases of Adie pupils, as miosis occurred simultaneously on the two sides and as, on the other hand, in cases of a postganglionic lesion the reaction should be less on the side of the lesion. We also could not find a stronger reaction to physostigmine on the side of the lesion in Adie's syndrome, but our experiments speak neither for nor against Adler and Scheie's conclusions, for our concentrations were much stronger than theirs. On the other hand, we do not doubt their statements, particularly the fact that they really observed pupillotonic reactions of peripheral origin. There are to be found in the literature a certain number of analogous observations; there were, for instance, 9 cases mentioned by Alajouanine and Morax in which pupillotonia developed secondarily after unilateral internal ophthalmoplegia with mydriasis and paralysis of accommodation. Axenfeld published a case in which some years after iridoplegia appeared pupillotonia developed; and there is further the interesting case observed by Garcin and Kipfer in which a neoplasm of the base of the skull gave rise to paralysis of the third nerve

with ptosis, mydriasis and absence of the light reflex. Four months later there was typical pupillotonia with mydriasis, absence of the reflex to light and sluggish though complete contraction on near vision but dilation on distant vision only after five to ten minutes. Six months later the pupil had become miotic and the reflex to light was still absent but there was no longer any symptom of the pupillotonia or of the eccentricity of the pupil observed in the former states.

There can, therefore, be no doubt that Adler and Scheie's observations are correct and that their supposition that pupillotonic reactions may be due to peripheral lesions of the third nerve is justified. They added to existing knowledge of pupillotonic reactions another and important new series of observations demonstrating that peripheral lesions of the third nerve may cause such reactions. They may be due both to postganglionic (Adler and Scheie, Axenfeld, Rothmann and others) and to preganglionic (Garcin and Kipfer) lesions of the third nerve.

Differential Diagnosis Between Lesions of the Third Nerve and Adie's Syndrome

	Lesions of Third Nerve	Central Sympathetic Lesions (Adie's Syndrome)
Sensory dilation of the pupil.....	+	+
Psychosensory phenomenon	+	—
Contractions with physostigmine.....	+ (except in cases of full destruction of third nerve)	+
Restoration with physostigmine of the reflex to light and to distant vision	—	+

But these pupillotonic reactions are not part of Adie's well defined syndrome. We never observed that physostigmine restored the pupil's ability to react to light in monkeys and in cats [9] when the third nerve was cut. In our experiments we generally observed after some months, when the third nerve had begun to regenerate, that the pupil dilated to sensory stimuli and that the psychosensory restitution phenomenon was present, increasing the still diminished, but to a certain degree restored, ability of the pupil to react to light. Physostigmine, however, contracted the pupil and diminished its capacity to react to light.

In cases of the real Adie syndrome, physostigmine also makes the pupil contract, but it regains its ability to react to light; the psychosensory restitution phenomenon, however, is absent, although the pupil dilates to sensory stimuli.

There are, therefore, great differences between the tonic pupil, possibly due to third nerve lesions, and the Adie pupil, due to a central sympathetic lesion, as shown in the accompanying table.

9. Our observations will be published in collaboration with Dr. M. B. Bender.

CONCLUSIONS

1. Pupillotonic reactions may be caused by peripheral lesions of the third nerve both postganglionic and preganglionic and by lesions in the great vegetative centers of the diencephalon and their connections with the mesencephalon.

2. Adie's syndrome is due to heredodegenerative disease localized in the great autonomic centers of the diencephalon and their connections with the mesencephalon. It is characterized by pupillotonic reactions with irritative (not paralytic, like the Horner-Bernard syndrome) sympathetic symptoms and absence of tendon reflexes. It generally has no syphilitic etiologic factor but as a syndrome may be produced by so-called asymptomatic syphilis nervosa.

3. As the nervous manifestations of congenital syphilis (more frequently than of acquired syphilis) are frequently localized in the sympathetic center, there is a possibility that in some cases Adie's syndrome is due to congenital syphilis.

4. The pupillographic picture of Adie's syndrome is generally unequivocal.

5. Physostigmine contracts the Adie pupil like the normal pupil; however, it restores the ability of the Adie pupil (in twelve to twenty minutes after its local application) to react to light and to dilate to distant vision.

6. The physostigmine test in cases of questionable diagnosis enables one to differentiate Adie's syndrome from similar syndromes due to acquired syphilitic infection.

7. Neurotonia characterized by a prompt contraction of the pupil to light but a sluggish and retarded dilation (sometimes after a latency period of more than five minutes) and by a convergence reaction which may be unilaterally or bilaterally diminished or absent appears to be an inversion of Adie's syndrome. The relation with Adie's syndrome is shown by the fact that either syndrome may be substituted for the other in the hereditary sequence; therefore, the basic processes must be considered identical.

8. The clinical entities of neurotonia and pupillotonic pseudotabes include many minor and abortive forms which can be detected by pupillography; they are not rare but are rather frequent anomalies and have the value of a focal stigma degenerationis in the nervous system.

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Ophthalmologic Reviews

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HEMORRHAGE AFTER CATARACT EXTRACTION

A CLINICAL AND EXPERIMENTAL INVESTIGATION OF ITS CAUSE AND TREATMENT

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Postoperative hemorrhage following cataract extraction has long been recognized as one of the more common accidents that may disturb an otherwise uneventful convalescence. The reported incidence of its occurrence varies from 1 to 35 per cent, the extremes representing, perhaps, differences in technic and skill or, more probably, differences in the manner in which examinations were made and recorded.

At the Institute of Ophthalmology it was felt that such hemorrhage was occurring with more than the usual frequency. Accordingly it was decided to investigate a series of consecutive cataract operations from a number of different aspects to determine (*a*) the true incidence of this complication and, (*b*) whether any contributing factor or factors could be discovered. If such factors could be discovered, more logical treatment or preventive measures could obviously be initiated. Four hundred and fifty-three cases were studied and the following points investigated: (1) incidence, (2) severity of hemorrhage, (3) time of hemorrhage, (4) age of patient, (5) seasonal incidence, (6) comparison between ward and private patients, (7) blood pressure, (8) diabetes, (9) syphilis, (10) intraocular pressure, (11) trauma, (12) pain, (13) type of operation, (14) iridectomy, (15) sutures, (16) retrobulbar injection, (17) skill of surgeon, (18) vitamin C nutrition, (19) capillary fragility and (20) prothrombin and vitamin K.

In addition, the literature relating to the physiologic and clinical features of blood clotting was reviewed, particular attention being paid to the merits of the so-called hemostatics.

Submitted in partial fulfilment of the requirements for the degree of Doctor of Medical Sciences in the Faculty of Medicine, Columbia University.

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PART I: CLINICAL INVESTIGATION OF 453 CASES OF CATARACT EXTRACTION

Incidence.—As has been stated, the literature reveals a wide variation in the incidence of postoperative hyphemia ranging from 1 to 35 per cent.[1] Some observers have not recorded the postoperative occurrence

1. (*a*) Wheeler, J. M.: A Study of Hemorrhage into the Anterior Chamber Subsequent to Operation for Hard Cataract, Tr. Am. Ophth. Soc. **14**:742, 1916. (*b*) Marshall, C. D.: On the Immediate and Remote Results of Cataract Extraction, Roy. London Ophth. Hosp. Rep. **14**:56, 1895. (*c*) Derby, H.: Report on Sixty-Four Cataract Extractions According to the Method of von Graefe, Arch. Ophth. **3**:74, 1873; (*d*) One Hundred Cases of Cataract Extractions with a Single Failure, with a Discussion of Advantages of Non-Anesthesia in This Operation, Tr. Am. Ophth. Soc. **3**:195, 1881. (*e*) Franke, E.: On the Extraction of Cataract According to Jacobson's Method, Arch. Ophth. **10**:121, 1881. (*f*) Strawbridge, G.: Report of Two Hundred and Sixty-One Cases of Cataract Extractions, Tr. Am. Ophth. Soc. **4**:298, 1885. (*g*) Vail, D.: On the Mechanism and Causes of Hyphema After Cataract Extraction, Am. J. Ophth. **24**:922, 1941. (*h*) Arnold, T.: Mitteilungen über vier hundert Staroperationen, Arch. f. Augenh. **25**:41, 1892. (*i*) Köllner, H.: Erfahrungen an 1,284 Kataraktextractionen mit Iridektomie, Ztschr. f. Augenh. **15**:506, 1906. (*j*) Schreiber, L.: Bemerkungen über die Kataraktextractionen in den Jahren 1893/96, Jahresb. ü. d. Leistung. d. Ophth. **27**:98, 1896. (*k*) Uhthoff, W.: Cataract Operations in Diabetics, Arch. Ophth. **38**:49, 1909. (*l*) Knapp, H.: Bericht über hundert Staarextractionen nach der neuen von Graefe'schen Methode eingeführt, Arch. f. Ophth. **13**:85, 1867; Bericht über ein zweiter Hundert Staarextractionen durch den Linearschnitt im Scleralbord, ibid. **14**:285, 1868; Bericht und Bemerkungen über ein drittes Hundert Staaroperationen nach der peripherlinearen Extractionsmethode, Arch. f. Augen- u. Ohrenh. **1**:44, 1869-1870; translated, Arch. Ophth. **1**:103, 1869; Bericht und Bemerkungen über ein viertes und fünftes Hundert Staarextractionen nach Gräfes Methode, Arch. f. Augen- u. Ohrenh. **6**:314, 1877; translated, Arch. Ophth. **6**:3, 1877; Bericht über ein sechstes Hundert Staarextractionen, Arch. f. Augenh. **8**:378, 1879; translated, Arch. Ophth. **8**:200, 1879; Report of a Seventh Hundred of Cataract Extractions, with Historical and Critical Remarks, Particularly on the Peripheral Opening of the Capsule, ibid. **10**:295, 1881; Report of the Eighth Series of One Hundred Consecutive Cataract Extractions, with Remarks, ibid. **12**:69, 1883; Cataract Extraction, Without Iridectomy, ibid. **16**:54, 1887; Report on the First Series of One Hundred Cataract Extractions Without Iridectomy, ibid. **17**:51, 1888; Report on a Second Series of One Hundred Successive Cataract Extractions Without Iridectomy, ibid. **18**:1, 1889; Report of a Third Series of One Hundred Cataract Extractions Without Iridectomy, ibid. **19**:280, 1890. (*m*) Vail, D., Jr.: Hyphema After Cataract Extraction, Tr. Am. Ophth. Soc. **31**:496, 1933. (*n*) Philps, A. S.: Post-Cataract Hyphaema, Brit. J. Ophth. **24**:122, 1940. (*o*) Berens, C., and Bogart, D.: Certain Postoperative Complications of Cataract Operations, with Especial Reference to Study of 1,004 Operations, Am. J. Surg. **42**:38, 1938. (*p*) Stallard, H. B.: A Corneo-Scleral Suture in Cataract Extractions: Its Technique and Advantages, Brit. J. Ophth. **22**:269, 1938. (*q*) Davis, F. A.: Personal Experiences with Intracapsular Cataract Extractions, Arch. Ophth. **19**:867 (June) 1938. (*r*) Wright, R. E.: Lecture on Cataract

of blood in the anterior chamber as hemorrhage unless it was severe enough to disrupt the wound. Lesser bleeding passed unnoticed. As Vail [1m] has stated, in a small series of cases carefully observed and recorded the frequency of hemorrhage is apt to be greater than in a larger series less carefully watched. For this reason an attempt to obtain an average by compilation of figures in the literature is meaningless.

For the purpose of this investigation bleeding which occurred at the time of operation was not included in the term "postoperative bleeding." Dressings were changed usually at two day intervals. Consequently, blood present in the anterior chamber at the time of the first dressing was not considered a result of postoperative bleeding unless obviously of recent origin. Any sign of increased or new hemorrhage on subsequent dressings was recorded as postoperative bleeding. Van Lint [2] has stated that blood present in the anterior chamber on the first dressing is usually due to the immediate bleeding from the section and is increased if the section is deep. He further stated that blood appearing after the eighth day is frequently a harbinger of iritis.

Of the present series of 453 cases, postoperative hemorrhage into the anterior chamber, the vitreous or both developed in 95, or 20.9 per cent. In many cases this was mild and in several it was expulsive in type, but all the cases were grouped under the general heading of postoperative bleeding even though the hemorrhage was perhaps not always initiated by the same mechanism.

Severity of Hemorrhage.—An arbitrary classification of the extent of bleeding was established: (*a*) slight—3 mm. or less of hyphemia (44 patients, or 46.3 per cent of the 95 patients who bled); (*b*) moderate—from 3 mm. of hyphemia to filling of the anterior chamber with blood but with the wound intact (34 patients, or 35.8 per cent); (*c*) severe—

Surgery, Am. J. Ophth. **20**:248, 1937. (*s*) Lehrfeld, L., and Donnelly, E. J.: Corneoepiscleral Suture in Cataract Extraction, Arch. Ophth. **24**:401 (Aug.) 1940. (*t*) McLean, J. M.: A New Corneoscleral Suture, ibid. **23**:554 (March) 1940. (*u*) Leech, V. M., and Sugar, H. S.: Reduction of Postoperative Complications in Cataract Operations with Corneoscleral Sutures, ibid. **21**:966 (June) 1939. (*v*) Vogt, A.: Zur Stardiskussion in Heidelberg, Klin. Monatsbl. f. Augenh. **101**:530, 1938. (*w*) von Herrenschwand, F.: Die Wundsprengung nach Altersstar-Extraktion und ihre Verhütung durch die Anlegung eines vorbereitenten Bindehautlappens, Ztschr. f. Augenh. **83**:87, 1934. (*x*) Kawahara, G.: Ueber die Vorder-Kammerbildung und Vorder-Kammerbildungblutung nach Kataraktextraktion, Zentralbl. f. d. ges. Ophth. **31**:693, 1934. (*y*) Reiser, K.: Unsere Erfahrungen mit der intracapsularen Starextraktion, Klin. Monatsbl. f. Augenh. **101**:692, 1938. (*z*) Schmidt, K.: Prognose der Operationsmöglichkeit bei verschiedenen Starformen, ibid. **96**:118, 1936.

2. Van Lint, A.: Extraction extracapsulaire de la cataracte complications postopératoires, in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 7, p. 650.

the wound bulging or open with blood on the dressing (12 patients, or 12.6 per cent); (*d*) expulsive (3 patients, or 3.2 per cent [0.65 per cent of all patients studied]).

Time of Hemorrhage.—All authors are in agreement that the fourth to the sixth day is the most likely time for spontaneous hemorrhage to occur. There is no such unanimity as to why this should be so. Collins [3] and Henderson [4] have shown that it is at about this time that blood vessels have grown across the wound, and Worth [5] has stated that some jar, movement or squeezing of the lids causes a rupture of the wound

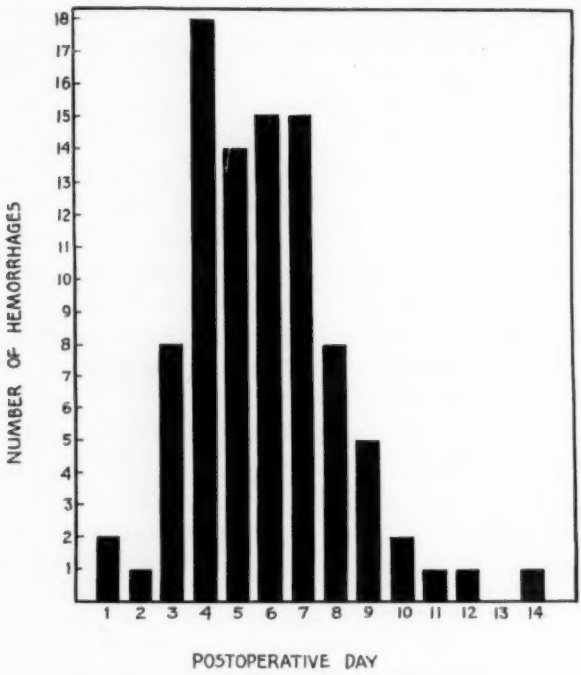

Chart 1.—Time of hemorrhage.

and tearing of these newly formed capillaries. In this respect the present series of cases proved no exception. As demonstrated in chart 1, the peak in the incidence of hemorrhage occurred on the fourth day, although a high frequency was observed until the seventh day. Routinely the patients were allowed out of bed on the fifth day; since

3. Collins, T.: Postoperative Complications of Cataract Extraction, Tr. Ophth. Soc. U. Kingdom **34**:41, 1914.

4. Henderson, T.: A Histological Study of the Normal Healing of Wounds After Cataract Extraction, Ophth. Rev. **26**:127, 1907.

5. Worth, C., in discussion on Collins,[3] p. 67.

hemorrhage was frequent at this time a possible causal relationship was suspected. While it is true that hemorrhage frequently occurred on the fifth day, it occurred even more frequently on the fourth day. In a number of patients who were allowed out of bed on the first or the second postoperative day, hemorrhage appeared as usual on the fourth or fifth day. There is no doubt that the increased freedom usually allowed at this time is a contributory factor, but it is questionable whether it is of much importance.

Age of Patient.—Wheeler,[1a] finding hemorrhage most common among patients aged 40 to 50, attributed this frequency to the greater activity of these patients and the attendant greater likelihood of self injury. Vail [6] stated the belief that age is not of much importance but found that hemorrhage usually occurred in persons past 50. Other

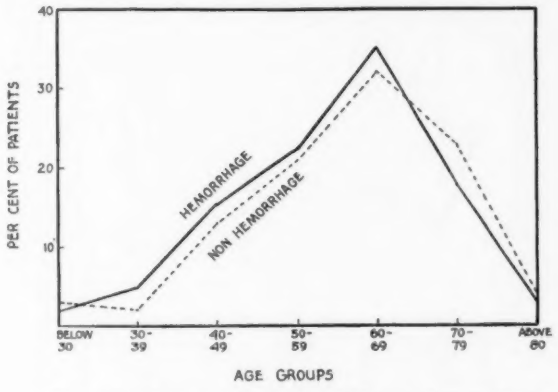

Chart 2.—Age groups and relation to hemorrhage.

investigators [7] have said that age is not significant. This assumption is in accord with my figures, which show equivalent distribution of hemorrhage and absence of hemorrhage in each age group (chart 2).

Incidence in Ward and in Private Patients.—It was felt that by and large private patients should be better nourished and prepared than ward patients. Analysis of this point is complicated by the fact that all private patients were operated on by the attending staff, whereas most of the ward patients were operated on by the resident staff. Forty-four per cent of the patients without complications were ward patients, and 56 per cent were private patients. Of those patients who bled, 59 per cent were ward and 41 per cent were private patients. These figures suggest that bleeding is more likely to ensue in ward than in private

6. Vail, footnote 1 *g* and *m*.

7. Jensen, V.: Hemorrhages into the Anterior Chamber of the Eye in Cataract Operation With and Without the Use of Adrenalin, Acta ophth. **10**:382, 1932.

patients, but since several variables were present an exact interpretation is difficult and no definite conclusion is drawn.

Seasonal Incidence.—Vail stated that the seasonal incidence is of no significance, but most authors have nothing to contribute on this point. My figures show a fair correlation between the number of cases of hemorrhage and the number of operations performed during any given month. The conclusion is that there is no relation between the time of year and the incidence of postoperative hemorrhage (chart 3).

Blood Pressure.—Many physicians [8] have stated the belief that vascular hypertension, and particularly a high diastolic pressure, encourages bleeding. They have urged that steps be taken to control the pressure, using such means as rest in bed, administration of sedatives and phlebotomy. Others [9] have denied that hypertension is of impor-

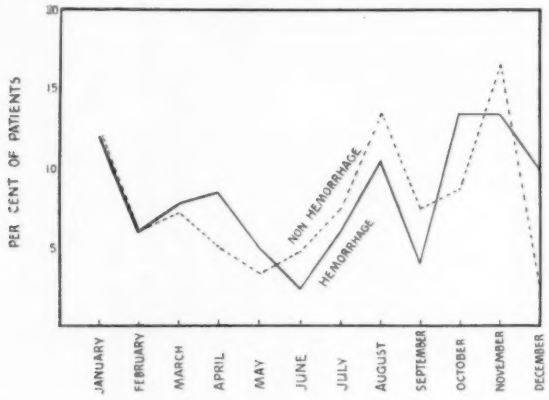

Chart 3.—Seasonal incidence of operations and hemorrhage.

tance. The present cases were analyzed separately with respect to the systolic and the diastolic pressure. As indicated in the graphs, there was no greater tendency for bleeding to occur in the hypertensive than in the normal patients (charts 4 and 5). Furthermore, there was no greater proportion of hypertensive patients among those patients with moderate or severe bleeding than among those with slight hemorrhage.

8. (*a*) Focosi, M.: Sul comportamento della pressione arteriosa durante alcuni interventi chirurgici oculair: Utilita ed cazione del salasso; sulla patogenesi di alcune complicazioni operatorie, Boll. d'ocul. **18**:689, 1939; abstracted, Am. J. Ophth. **23**:1412, 1940. (*b*) Kirby, D. B.: Prevention and Handling of Complications Arising During and After Cataract Extraction: Some Practical Points, Arch. Ophth. **25**:866 (May) 1941. (*c*) Berens and Bogart.[10] (*d*) Lint.[2]

9. (*a*) Gifford, S. R.: The Prevention of Complications in the Cataract Operation, Illinois M. J. **68**:243, 1935. (*b*) Carle, T.: Ueber postoperative Kammerblutungen bei intrabulbären Eingriffen, Acta ophth. **10**:242, 1932. (*c*) Vail.[6] (*d*) Philps.[11]

The three patients with expulsive hemorrhage had blood pressure of 180 systolic and 105 diastolic, 170 systolic and 50 diastolic and 140 systolic and 96 diastolic, respectively.

Diabetes.—In general diabetic patients are considered poorer risks as far as potential hemorrhage is concerned, but, again, there is a difference of opinion as to whether or not this disease increases the incidence of bleeding after cataract extraction. Wheeler [1a] found bleeding in about 29 per cent of his diabetic patients but in only 4.57 per cent of his entire group. He found that the amount of sugar in the urine apparently made little difference but stated the belief that the presence of diabetes of any degree of severity was an important predisposing

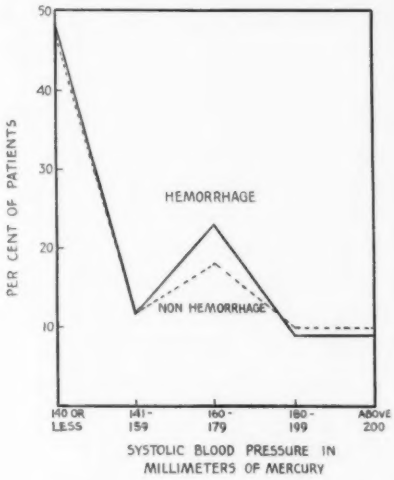

Chart 4.—Relation of systolic blood pressure to hemorrhage.

factor. Kirby,[8b] Wright [1r] and Berens and Bogart [1o] agreed. On the other hand, Marshall,[1b] reporting 1,519 cataract operations, had 30 diabetic patients in the series, in none of whom hemorrhage developed. Uhthoff [1k] reported on a group of 115 diabetic patients in whom extractions were performed with an incidence of hemorrhage of 8.9 per cent. This incidence compared favorably with his own figures for nondiabetic patients. Philps [1n] found the same proportion in diabetic and in nondiabetic patients but noted that of 4 patients who bled from the iris, as distinguished from the wound, 3 were diabetic. He expressed the opinion that most postoperative bleeding occurs from the wound but that diabetic patients are prone to bleed from the iris.

In the present series there were 40 diabetic patients, 9, or 22.5 per cent, of whom had hemorrhage. This was slight in 6 and severe in 3 and interfered with the ultimate visual result in none. It was therefore

concluded that the presence of diabetes does not alter the prognosis greatly as far as postoperative bleeding is concerned.

Syphilis.—Seven patients had a positive Wassermann reaction; hemorrhage developed in only 1. No significance was attached to this factor.

Intraocular Pressure.—In general increased intraocular pressure is thought to predispose to postoperative hemorrhage and particularly to the expulsive type. In the present series 8 patients had a pressure

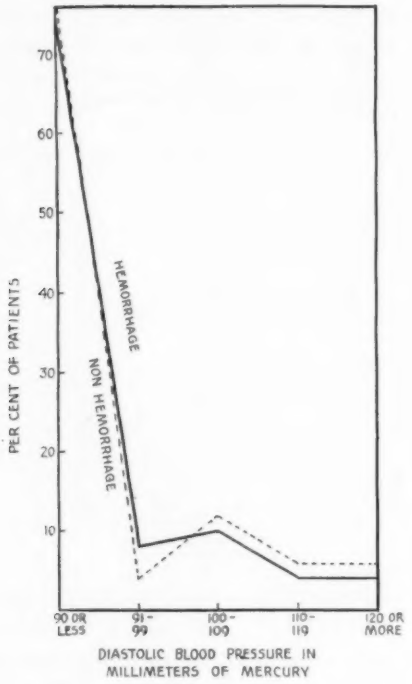

Chart 5.—Relation of diastolic blood pressure to hemorrhage.

of about 30 mm. (Schiøtz). Two of these had hemorrhage. None of the patients with expulsive hemorrhage had elevated pressure. This number is too small to permit statistical conclusions, but at least there is no evidence to suggest that increased intraocular pressure is an unfavorable sign with respect to the subsequent development of bleeding.

Trauma.—Herman Knapp [11] in 1869 stated that he was convinced that in a large number of cases after-hemorrhage is traumatic in origin, being chiefly due to the patient's unconsciously rubbing his eye; but he also stated that some, and usually the worst, hemorrhage is from another and unknown source. Other authors, including Vail, Philps,

Berens and Bogart, Stallard, Van Lint, Worth and Kirby, have agreed that trauma plays an important part.

In only 8, or 8.4 per cent, of the present series of cases could a definite history of trauma be linked to postoperative bleeding. In 3 cases blood was seen to appear in the anterior chamber during the removal of sutures. Two patients struck their dressings accidentally and noted immediate pain. One experienced sudden sharp pain while sneezing and another while blowing his nose forcibly. Presumably their actions were accompanied by involuntary squeezing of the lids, which produced a disruption of the wound. In 8 more cases, although no specific history of trauma could be elicited, certain complications, such as postoperative psychosis, vomiting and distention occurred, during which it is possible that patients might have inadvertently traumatized their eyes.

Pain.—In 47, or one-half the patients, pain varying in type from mild to severe was associated with the onset of the bleeding. However, 5 of those with very severe bleeding noted no pain at all.

Type of Operation.—Some investigators have found an increased tendency to bleeding after intracapsular extraction as compared with the extracapsular technic.[17] The following tabulation indicates that in the present series no difference could be found in the bleeding propensity after any particular type of lens delivery with the possible exception of loop extraction. In cases in which such extraction was employed there were as a rule complications and difficulties.

Type of Operation	No Hemorrhage	Hemorrhage
Extracapsular	130 (36.3%)	34 (35.8%)
Intracapsular	183 (51.1%)	47 (49.4%)
Attempted Intracapsular	37 (10.3%)	11 (11.5%)
Loop	5 (1.4%)	4 (4.2%)
Linear	3 (0.8%)	

Iridectomy.—Wheeler stated the belief that the presence or absence of iridectomy during a cataract extraction is of considerable importance in the later development of bleeding. He observed hemorrhage in 3.12 per cent of cases of extraction after iridectomy, in 3.97 per cent of cases of simple extraction and in 6.94 per cent of cases of extraction with iridectomy. Without actually making a statement, he implicated the iris as the source of bleeding. Worth's [5] opinion that hyphemia results from the tearing of new-formed vessels at the site of the section, Wheeler [18] stated, "is not in accord with that held by most observers, who believe that hemorrhages come from the iris."

Vail stated the belief that the lessened incidence in cases of extraction after preliminary iridectomy may be due to the greater tendency to performance of corneal section in these cases and disagreed with the assumption that the iris is an important source of postoperative bleeding.

Philps [1n] recorded every case of hyphemia in the wards of two London hospitals during 1937 and 1938. Among 374 extractions 49 hemorrhages occurred, an incidence of 13.13 per cent. Practically identical figures were found for extractions done with iridectomy, for those done without iridectomy and for those done after iridectomy.

Wright [1r] expressed the opinion that certain rigid irises are apt to bleed and that the normal iris does not bleed. He said that when there are diseased vessels, as in arteriosclerosis and diabetes, the complication of postoperative hemorrhage is more likely to occur.

Elschnig [10] has stated that bleeding comes from the iris vessels infrequently and then only when the iridectomy has been done so far posteriorly as to injure the ciliary body or when an inflammatory process has increased the number of vascular channels in the iris.

My figures show that the performance of an iridectomy does increase somewhat the incidence of hemorrhage:

Type of Operation	No Hemorrhage	Hemorrhage
Complete iridectomy	218 (60.9%)	72 (75.7%)
Peripheral iridectomy	55 (15.4%)	17 (17.9%)
Preliminary iridectomy	38 (10.6%)	0 (0%)
No iridectomy	13 (3.6%)	2 (2.1%)
Iridotomy	34 (9.5%)	4 (4.2%)

The complete absence of hemorrhage among the 38 cases in which a preliminary iridectomy was performed suggests that if hemorrhage is anticipated, for example because of its occurrence in a previous operation, it might be better judgment to perform a preliminary iridectomy.

Sutures.—The presence or absence of sutures as a factor influencing postoperative bleeding has recently been much discussed. Vail in 1933 stated that theoretically conjunctival sutures could be the cause of hemorrhage by stretching the wound edges. Stallard [1p] stated that prior to his adoption of a single mattress corneoscleral suture, postoperative hyphemia occurred in 30 to 35 per cent of all the patients he operated on for cataract at Moorfields. After the introduction of this suture, however, 107 consecutive patients were operated on without a single hemorrhage. Using this same type of suture, Philps has reported 120 consecutive patients operated on without hemorrhage. Peter [11] has said: "I am not sure that any form of suture will prevent hyphemia whether the suture be wholly conjunctival or corneoscleral conjunctival.

10. Elschnig, A.: Kritischer Bericht über das Schrifttum 1934 bis einschliesslich 1938, Zentralbl. f. d. ges. Ophth. **43**:321, 1939.

11. Peter, L. C.: Sutures in Cataract Extraction, Tr. Am. Ophth. Soc. **45**:46, 1941.

I cannot make up my mind that the suture plays any role in preventing prolapse." He said that he preferred the suture described by Stallard. Ellett,[12] discussing Peter's paper, said: "The freedom from postoperative anterior chamber hemorrhage which Mr. Stallard has enjoyed since adopting this suture has, I am sorry to say, not been my fortune.—I see hemorrhage with unpleasant frequency in spite of this or any other form of suture." Castroviejo,[13] who used three interrupted corneoscleral sutures, stated the belief that the use of this type of suture has not lessened the incidence of hemorrhage in his cases but that it greatly minimizes the danger of astigmatism and iris prolapse. On the other hand, many other surgeons, including Verhoeff,[14] McLean,[1t] Kirby,[8b] Lehrfeld and Donnelly [18] and Leech and Sugar,[1u] have said that the use of a corneoscleral suture reduces the incidence of postoperative hyphemia.

As indicated in the following tabulation, no significant differences could be found with respect to sutures in the present cases:

Suture	No Hemorrhage	Hemorrhage
Corneoscleral	204 (57.3%)	56 (59.0%)
Conjunctival	147 (41.3%)	38 (40.0%)
None	5 (1.4%)	1 (1.0%)

Retrobulbar Injection.—Van Lint [2] quoted Hambresin to the effect that retrobulbar injection, and particularly the injection of epinephrine hydrochloride, is an explanation for the increased frequency with which postoperative hemorrhage is encountered. The instillation of epinephrine hydrochloride into the conjunctival sac has also been questioned as a cause of later hemorrhage. In 1925 Luundsgaard introduced instillation of epinephrine hydrochloride into the ophthalmic clinic at Copenhagen, Denmark. Among the first 60 patients operated on, 3 had choroidal hemorrhage, whereas this complication had occurred previously only twice among 1,200 patients operated on by the same surgeon. Instillation of epinephrine hydrochloride was therefore stopped. Among the next 400 patients no choroidal hemorrhage appeared, and there was a slight decrease in the number of cases of hemorrhage in the anterior chamber. Jensen,[7] working in the same clinic, then reviewed 80 cases of extracapsular extraction with complete iridectomy, in half of which the patient was given instillations of epinephrine hydrochloride. He concluded that the use of epinephrine hydrochloride is unimportant, that with its use there is less bleeding at the time of operation but more delayed bleeding. Carle,[9b] after investigating 267 combined extractions,

12. Ellett, E. C., in discussion on Peter.[11]

13. Castroviejo, R.: Personal communication to the author.

14. Verhoeff, F. H.: A Corneoscleral Suture in Operations for Cataract, Tr. Am. Ophth. Soc. **25**:48, 1927.

came to the conclusion that the instillation of epinephrine hydrochloride has had no effect on the frequency of hemorrhage in the anterior chamber.

Since all the patients in the present series received instillations of epinephrine hydrochloride, I can draw no conclusions on this point. All, however, did not receive retrobulbar injections:

	No Hemorrhage	Hemorrhage
Injection	139 (39%)	35 (36.9%)
No injection	217 (61%)	60 (63.1%)

Bleeding occurred as frequently without as with the use of retrobulbar injection.

Surgeon.—On the assumption that the skill of individual surgeons varies and that perhaps increased trauma at the time of operation might predispose to later hemorrhage, the records of individual surgeons were examined. No significant variations were found. The surgeons doing the most operations had the greatest number of cases in which hemorrhage occurred; the rest had such cases in proportion to the number of cataracts extracted. It is true that the patients operated on by the resident staff showed a somewhat greater frequency of postoperative bleeding as compared with those operated on by the attending staff, but, as pointed out previously, this situation is complicated by the fact that in general the patients operated on by the residents were not as well nourished and prepared as the private patients.

Vitamin C.—It has long been known that a serious deprivation of vitamin C results in bleeding from various tissues. Höjer [15] observed that ascorbic acid is intimately concerned with the synthesis and maintenance of the intercellular supporting materials which provide the framework for healing. It is also of importance in the formation of all nonepithelial cement substances, including the intercellular substances of the capillary walls.[16] Man is thought to be incapable of synthesizing vitamin C, and there is probably little or no storage in the human body.

In the full grown adult the daily vitamin C requirement is said to be independent of age, weight and height.[17] The necessary level in the blood to produce saturation of the tissues and the blood is 1 mg. per hundred cubic centimeters. A daily intake of about 100 mg. in a normal person will produce this level. With this amount ingested, about 85 to 90 mg. will be retained and 10 to 15 mg. excreted. When more than 100 mg. is fed the excretion rises immediately and the plasma level

15. Höjer, J. A.: Studies in Scurvy, Acta pædiat. **3**:8, 1924.

16. Abt, A. F., and Farmer, C. J.: Vitamin C: Pharmacology and Therapeutics, J. A. M. A. **111**:1555 (Oct. 22) 1938.

17. Ralli, E. P.; Friedman, G. J., and Sherry, S.: Vitamin C: Requirements in Man, J. Clin. Investigation **18**:705, 1939.

gradually; 0.4 to 0.5 mg. per hundred cubic centimeters of plasma is generally considered the lower limit of normal. At this level the tissues are not saturated, and active scurvy appears at or about this point.

Various methods have been devised for determining the vitamin C storage. Among them is the intradermal injection of 2,6-dichlorophenol-indophenol [18] with observation of the length of time taken for the blue wheal to disappear. This method does show statistical differences, but the scattering of the figures destroys its usefulness in individual cases.

The daily urinary excretion has been followed, but other factors, such as renal function, complicate the interpretation.

Saturation tests and urinary tolerance tests are reliable but long drawn out and time consuming.

Capillary fragility has been said by Wright and others [19] to parallel vitamin C nutrition. By other investigators, no such parallelism has been found.[20] In this connection the existence of vitamin P, which has been thought to influence capillary fragility independently of vitamin C subnutrition, has been debated and not as yet generally accepted.[21]

The vitamin C level in the plasma is a measure of the immediate nutritive state and may be low when there is still considerable vitamin in the tissues. The recent work of Crandon, Lund and Dill [22] casts some doubt on the reliability of the present tests of ascorbic acid. One of these authors remained on a diet totally lacking in vitamin C for one

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18. Kajdi, L.; Light, J., and Kajdi, C.: A Test for the Determination of Vitamin C Storage; Vitamin C Index, J. Pediat. **15**:197, 1939. Rapaport, H. G., and Miller, S. H.: The Determination of Vitamin C in Children by Intradermal Injection, ibid. **15**:503, 1939.

19. (*a*) Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936. (*b*) Göthlin, G. F.: When Is Capillary Fragility a Sign of Vitamin C Subnutrition in Man? Lancet **2**:703, 1937. (*c*) Sloan, R. A.: Comparison of Methods for Detecting and Grading Subclinical Scurvy, J. Lab. & Clin. Med. **23**:1015, 1938.

20. (*a*) Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic Acid Determinations in Blood Plasma and Their Relationship to Capillary Fragility, J. Pediat. **8**:1, 1936. (*b*) Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**:353, 1940.

21. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610, 1938. Bentsath, A.; Rusznyak, S., and Szent-Györgi, A.: Vitamin Nature of Flavones, Nature, London **138**:798, 1937; Vitamin P, ibid. **139**:326, 1937; **140**:426, 1937. Jersild, T.: Therapeutic Effect of Vitamin P in Schönlein-Henoch Purpura, Lancet **1**:1445, 1938. Ivy, A. C., and Gray, J. S.: The Application of Recent Contributions in Basic Medical Sciences to Surgical Practice: Vitamin P and Capillary Fragility, Internat. Abstr. Surg. **69**:1939; in Surg., Gynec. & Obst., July 1939.

22. Lund, C. C., and Crandon, J. H.: Human Experimental Scurvy and the Relation of Vitamin C Deficiency to Postoperative Pneumonia and to Wound Healing, J. A. M. A. **116**:663 (Feb. 22) 1941. Crandon, Lund and Dill.[20b]

hundred and thirty-two days before the first clinical signs of scurvy appeared, namely hyperkeratotic papules. One hundred and sixty-one days elapsed before the perifollicular hemorrhages of scurvy appeared. A plasma ascorbic acid level of zero, obtained with several laboratory methods, including that of Farmer and Abt, was present for thirteen weeks prior to the onset of clinical symptoms. Adequate wound healing following a biopsy was found forty-four days after the zero level was first obtained. With total vitamin C deficiency, failure in healing did occur and was manifest microscopically by a lack of intercellular substance. This substance reappeared within ten days after the parenteral administration of ascorbic acid. The authors stated the belief that the best index of vitamin C nutrition is the level present in the white cell and platelet layer of centrifuged blood. Immediately after the ingestion of cevitamic acid the plasma level may be high, but it is generally felt that a morning determination of the plasma during fasting is a fairly reliable index of the vitamin C nutrition.

Lanman and Ingalls [23] have shown that scurvy in the guinea pig interferes with wound healing. Deficiency in vitamin C has also recently been investigated [24] as a possible cause for the appearance of wound rupture and evisceration after abdominal operations, without definite conclusions being reached. Urbanek and Albrecht [25] stated the belief that there is less likelihood of hemorrhage after an intraocular operation when the patient is saturated with vitamin C. Bartlett, Jones and Ryan,[26] accepting 0.5 to 1.3 mg. per hundred cubic centimeters as the normal limits of cevitamic acid, investigated 188 surgical patients at the Massachusetts General Hospital and observed that two thirds had plasma levels of 0.5 mg. per hundred cubic centimeters or less. They stated the belief that the optimal state of vitamin C nutrition is obtained by only a small percentage of the population. Holman,[27] similarly, found 44 per cent of free clinic patients at the Stanford University Hospitals to be on diets low in vitamin C. Nine of 70 patients were on the borderline of scurvy. The cevitamic acid nutrition has been demonstrated to be lower in cataractous than in noncataractous patients.[28]

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23. Lanman, I. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Ann. Surg. **105**:616, 1937.

24. Hartzell, J. B.; Winfield, J. M., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, J. A. M. A. **116**:669 (Feb. 22) 1941. Hunt, A. H.: Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436, 1941.

25. Urbanek, J., and Albrecht, W.: C Vitamin und Lebensalter, Ztschr. f. Augenh. **95**:129, 1938.

26. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C Studies in Surgical Patients, Ann. Surg. **111**:1, 1940.

27. Holman, E. F.: Vitamins and Protein Factors in the Preoperative and Postoperative Care of the Surgical Patient, Surg., Gynec. & Obst. **70**:261, 1940.

28. Abt and Farmer.[16] Urbanek and Albrecht.[25]

With these reports in mind it was decided to investigate the vitamin C nutrition of a group of cataractous patients to see whether or not any correlation could be observed between the incidence of postoperative hemorrhage and the vitamin C level in the blood plasma. In 136 patients this level was determined by titration with indophenol, a method, which while not specific for ascorbic acid because other constituents of body fluids are also reducing agents, is, nevertheless, with proper speed and choice of end points, satisfactory for determinations on blood.[29] As shown in chart 6, most of the patients had rather high levels of ascorbic acid, only 5 being found with levels below 0.5 mg. per hundred cubic centimeters. Of these 5, however, 4 had postoperative hemorrhage. Through the rest of the range the percentage of patients who bled and of those who did not bleed were close enough to preclude statistical differences. The conclusion drawn was that, whereas persons

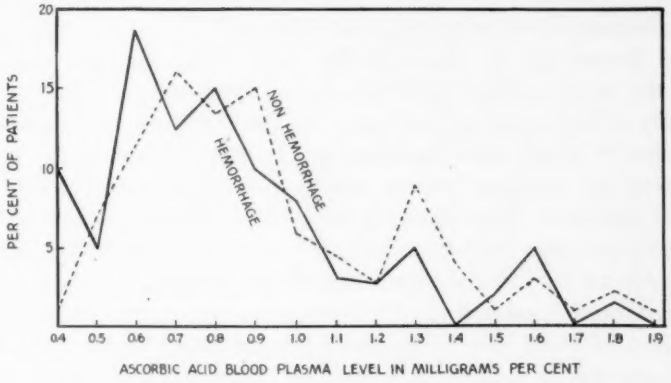

Chart 6.—Relation of vitamin C nutrition to hemorrhage.

in the prescurvy stage are more apt to have hemorrhage, those in the generally accepted normal range of 0.5 mg. or higher show the usual incidence of hyphemia. Bleeding was encountered in persons with the high ascorbic acid levels of 1.3 to 1.8 mg. per hundred cubic centimeters of plasma.

Capillary Fragility.—To determine whether or not clinical testing of capillary fragility might predetermine potential bleeders, such testing was carried out on 68 patients. Simultaneous vitamin C determinations were made for the same patients. In accordance with the instructions of Wright,[19a] a blood pressure cuff was applied to the upper arm and maintained at a pressure half way between the systolic and the diastolic pressure for fifteen minutes. For patients who could not stand the dis-

29. Field, H., Jr., and Melnick, D.: Clinical Determination of Vitamin Nutrition, J. Lab. & Clin. Med. **26**:45, 1940.

comfort, this time was shortened to seven and a half minutes. After removal of the cuff the cutaneous petechiae in a 2.5 cm. circle 4 cm. below the crease in the elbow were counted. More than twenty petechiae in a given area was considered evidence of capillary fragility.

On the opposite arm the fragility was tested by applying a negative pressure of 20, 30, 40 and 50 mm. of mercury to the skin of the forearm for one minute. This was done by means of a hand-operated suction pump to which a pressure gage was attached. More than twenty petechiae in a 1 cm. circle at a negative pressure of 30 mm. was taken as evidence of capillary weakness. In general it may be said that the results of these two tests frequently did not agree. With both, the non-bleeding patients showed a somewhat greater proportion of negative readings than did the patients who did bleed, but the individual variation was so great that the tests were clinically useless for the purposes of the study. Furthermore, no definite relation could be established between capillary fragility as determined by these methods and the plasma vitamin C level. Frequently the patients with the highest ascorbic acid levels showed the greatest number of petechiae. Seventeen, or 25 per cent, of the 68 patients had hemorrhage. All had vitamin C levels above 0.6 mg. per hundred cubic centimeters. It was concluded that present clinical tests for capillary fragility offer no help in predetermining post-operative hyphemia after cataract extraction. This conclusion is in accord with the work of Crandon, Lund and Dill, who found negative reactions to capillary fragility tests even in the presence of frank scurvy.

It would seem good judgment if for any reason the intake of vitamin C is suspected of being low or its absorption of being faulty to give the patient large amounts of ascorbic acid by mouth, parenterally or both prior to operation. The ascorbic acid should be given not only because of the possibility of capillary fragility but because of its demonstrated importance in wound healing. If, however, a patient is well saturated with vitamin C, further administration serves no useful purpose.

Prothrombin and Vitamin K.—The existence of vitamin K was suspected by Dam [30] in 1929 when in newly hatched chicks placed on a fat-free diet hemorrhages into the skin and mucous membranes developed. A voluminous literature has since appeared on this subject. Originally obtained by extraction of alfalfa and putrefied fish meal, this fat-soluble vitamin was subsequently isolated in crystalline form [31] and shown to be a substituted 1, 4 naphthoquinone. A number of other naphthoquinones have since been isolated and shown to have varying antihemorrhagic

30. Dam, H.: Cholesterinstoffwechsel in Hühnereiern und Hünchen, Biochem. Ztschr. **215**:475, 1929.

31. McKee, R. W.; Binkley, S. B.; MacCorquodale, B. W.; Thayer, S. A., and Doisy, E. A.: Studies in Vitamin K, J. Am. Chem. Soc. **61**:1295, 1939.

properties, among them being 2-methyl-1, 4 naphthoquinone, which has proved to be of high potency. Other substances are rapidly being synthesized and tested. Although the pharmacologic aspects have not yet been completely worked out, no toxic manifestations have been observed from small doses. Nausea and vomiting have been reported from oral doses of 3 mg. per kilogram of body weight.[32] In animals ten thousand times the therapeutic dose has caused hemolytic anemia.[33]

There is no endogenous production of vitamin K in the human body aside from bacterial putrefaction in the intestinal tract.[34] and there is as yet no proof that the product of this is absorbed. Normally vitamin K is found in the photosynthetic portion of plants and in some vegetable oils.

Prothrombin is now thought to be elaborated only in the liver.[35] It is assumed either that vitamin K is a building stone in the formation of prothrombin or that it is necessary in maintaining hepatic function. Being fat soluble, it is absorbed only in the presence of bile; consequently lack of bile in the intestinal tract for any reason, such as obstruction of the bile ducts, will eventuate in a deficiency of vitamin K and prothrombin. An inadequate diet and intestinal lesions which prevent the absorption of vitamin K, such as occur in association with surgical short-circuiting procedures, diarrheal disease and colitis, are common causes for vitamin K deficiency.

Four factors are therefore necessary to prevent hypoprothrombinemia: (1) normal bile in the intestinal tract, (2) a diet containing vitamin K or material from which it can be manufactured, (3) a normal absorptive surface in the small intestine and (4) an adequately functioning liver. It is now generally felt that there is no use in administering vitamin K unless there is a definite deficiency of prothrombin. Little has appeared in the ophthalmic literature concerning its use. Burch[36] has reported improvement in recurrent hemorrhagic retinitis. It has been thought

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32. Norcross, J. N., and McFarland, M. D.: Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia: Clinical Observations, J. A. M. A. **115**:2156 (Dec. 21) 1940.

33. Rhoads, J. E., and Fliegelman, M. T.: The Use of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Substitute) in Treatment of Prothrombin Deficiency in Patients, J. A. M. A. **114**:400 (Feb. 3) 1940.

34. Andrus, W. D.: Newer Knowledge of Vitamin K, Bull. New York Acad. Med. **17**:116, 1941. Smith, H. P.; Ziffren, S. E.; Owen, C. A., and Hoffman, G. R.: Clinical and Experimental Studies on Vitamin K. J. A. M. A. **113**:380 (July 29) 1939.

35. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma Prothrombin Observations After Total Hepatectomy in Dog, Am. J. M. Sc. **198**:193, 1941.

36. Burch, E. P.: Treatment of Hemorrhagic Retinitis with Vitamin K, Minnesota Med. **22**:32, 1939.

to lessen the incidence of retinal hemorrhages in the newborn when administered to the mothers shortly before labor.[37]

It is known that prothrombin is present in large physiologic excess, as much as an 80 per cent loss being necessary to produce hemorrhage. Consequently, on a priori grounds, the administration of vitamin K preoperatively to cataractous patients would not be expected to lessen the incidence of postoperative hemorrhage unless it could be shown that patients in the cataractous age group are more likely to have lowered prothrombin levels than other persons.

Twenty-one cataractous patients had their prothrombin levels determined by the method of Quick [38] on the day before operation. They were given 1 mg. of menadione (2-methyl-1, 4 naphthoquinone) by mouth then and daily for the succeeding ten days. This amount has been shown to be sufficient to raise the prothrombin level in a deficient patient in a short time. Bile salts were not administered concomitantly, because none of the patients were jaundiced or showed other evidence of deficient bile in the intestinal tract. Of the 21 patients, 13 had original levels of 80 per cent of normal or better. Only 1 patient had less than 55 per cent of normal, and his level was raised from 23 to 80 per cent at the end of ten days. Three, or 23 per cent, of the 13 patients with levels of 80 per cent or more had hemorrhage. Of the 8 patients with original levels below 60 per cent, 3 had hemorrhage. In all 8 the level was raised to 80 per cent or higher by the administration of vitamin K.

Since it was not feasible to make routine prothrombin determinations for a large series of patients, it was decided to give vitamin K by the method described to a series of cataractous patients, with the expectation that if prothrombin deficiency is an important factor in causing postoperative hemorrhage this would be reflected in a lessened incidence of such hemorrhage in the selected group as compared with the group as a whole. No such factor was found. One hundred and seventeen patients received vitamin K. Of these, 29, or 23.1 per cent, had hemorrhage, as compared with 19.6 per cent of those who did not receive vitamin K. Recently Foss [39] reported on a series of 48 patients with normal prothrombin times, as determined by a modification of Quick's method, on whom cataract operations were performed. Twelve, or 25 per cent, of these had hemorrhage either at the time of operation or later. The

37. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn Infant: IV. The Effect of Antenatal Administration of Vitamin K on the Incidence of Retinal Hemorrhage in the Newborn, Bull. Johns Hopkins Hosp. **68**:158, 1941. Pray, L. B.; McKeown, H. S., and Pollard, W. E.: Hemorrhagic Diathesis of the Newborn: Effect of Vitamin K Prophylaxis and Therapy, Am. J. Obst. & Gynec. **42**:836, 1941.

38. Quick, A. J.: The Clinical Significance of Prothrombin as a Factor in Hemorrhage, Pennsylvania M. J. **43**:125, 1939.

39. Foss, B.: Gibt es eine K Vitamininsufficienz bei Blutungen nach intrabulbären Eingriffen? Acta ophth. **19**:15, 1941.

author concluded that K avitaminosis is not a usual cause of bleeding after intraocular operations. He also found a normal amount of prothrombin in patients with retinal hemorrhage. Our findings, as well as those of Foss, are not in agreement with Kronfeld,[40] who stated that "in patients with unexplained postoperative hemorrhages but normal coagulation time, vitamin K has been used by a number of ophthalmologists with apparently beneficial results."

PART II: REVIEW OF PHYSIOLOGY OF BLOOD CLOTTING AND APPRAISAL OF HEMOSTATICS

Before an evaluation of the many methods which have been advocated to prevent or control hemorrhage is attempted, a brief review of the physiology of coagulation so far as it is known is presented. It should be understood that, although the basic facts are established, knowledge of the mechanism of the reactions involved during blood clotting is still largely theoretic.[41]

A dual defense against hemorrhage is recognized:[42] (*a*) the coagulability of the blood and (*b*) the vascular response to trauma. According to Quick, the latter is probably involved in more bleeding conditions than the former, but little is known about its fundamental factors. Macfarlane,[43] after studying injured living capillaries, made the following hypotheses:

A. After a wound, bleeding occurs from injured capillaries which are dilated under the influence of an H substance set free from damaged tissue.

B. When the H substance has been removed the capillaries contract and bleeding ceases, assistance possibly being provided by the agglutination of platelets.

C. The escaped blood has time to clot during the contractile phase.

D. Redilatation of the capillaries occurs, but the wound is now healed by the clot.

E. In punctured wounds the clot is not necessary, since the approximated edges are sealed during the period of capillary constriction.

This theoretic mechanism may fail at two points. There may be a loss of capillary contractility, which occurs in some hemorrhagic states, such as purpura. Secondly, when defective coagulation is present an

40. Kronfeld, P. C.: Clinical Aspects of Vitamin Deficiencies in Ophthalmology, Illinois M. J. **80**:298, 1941.

41. Eagles, H., in MacLeod, J. J. R.: Physiology in Modern Medicine, ed. 9, St. Louis, C. V. Mosby Company, 1941, p. 313.

42. Quick, A. J.: A Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Am. J. M. Sc. **199**:118, 1940.

43. Macfarlane, R. G.: Critical Review: The Mechanism of Hemostasis, Quart. J. Med. **37**:1, 1941.

insecure clot may form during the contractile phase. This occurs in hemophilia, fibrinopenia and hemorrhagic disease of the newborn. Quick stated the belief that there is so little known about the fundamental vascular response that the discussion or classification of such diseases as the purpuras should await the development of more knowledge.

The modern theory of blood coagulation stems from the work of many men, including Alexander Schmidt, Hamarsten, Bordet, Howell, Morawitz and Wohlisch. It assumes the presence of at least four factors in the circulating blood, fibrinogen, prothrombin, calcium and thromboplastin.

Fibrinogen is a plasma protein thought to be elaborated in the liver.[44] Occurring in plasma, lymph, chyle, exudates and transudates, it also plays a part in tissue repair work. When acted on by thrombin it is converted from a colloidal sol to an insoluble gel, fibrin. Platelets, attaching themselves to fibrin threads, bend and twist the strands, thus bringing about clot retraction. Its source and concentration have little influence on the clotting time.[45]

Prothrombin, the precursor of thrombin, is also elaborated in the liver [35] and is now thought to be a proenzyme closely associated with serum globulin. Infants are born with a normal amount of prothrombin, probably obtained from the maternal reserve.[46] Although there has been some disagreement among various workers, in general [47] it is felt that there is some decrease in plasma prothrombin during the first few days of life, the content rising gradually thereafter. The mechanism is uncertain and has been attributed to (*a*) the normal lack of bile for several days, which would prevent absorption of vitamin K; (*b*) deficiency in globulin and the fact that most infants are denied a rich source of globulin in colostrum, and (*c*) the absence in the intestinal tract until about the fifth day of the bacterial flora which normally produce vitamin K. Available reports suggest that the administration of vitamin K to mothers during or before labor is of value.[48] In adults the

44. Drury, D. R., and McMaster, P. D.: The Liver as the Source of Fibrinogen, J. Exper. Med. **50**:569, 1929.

45. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances, Am. J. M. Sc. **199**:181, 1940.

46. Grossman, A. M.: The Plasma Prothrombin Concentration in Normal Infancy, Thesis, Marquette University, Milwaukee, 1939.

47. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941.

48. Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn: Prematurity and Vitamin K, Bull. Johns Hopkins Hosp. **65**:138, 1939. Shettles, L. B.; Delfs, E., and Hellman, L. M.: Factors Influencing Plasma Prothrombin in the Newborn Infant: II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate, ibid. **65**:419, 1939.

prothrombin level is remarkably constant, and the substance is present in large physiologic excess, no serious hemorrhage occurring until a level of 20 per cent of normal is reached. With existing methods of estimating blood prothrombin a considerable margin of error exists. Butt and Snell [47] stated the belief that a value of less than 80 per cent of normal is significant and that values below 50 per cent of normal should be considered in the potential danger zone.

Regarding a thromboplastic factor, there is considerable evidence to show that plasma contains a dissolved substance which acts like platelet and tissue extract,[41] the importance of which is uncertain. In general, however, it is felt that thrombokinase does not occur free but is liberated by injured tissue cells and platelets. When tissue juices are not present it is derived from platelets alone. It occurs widely in the body but is especially plentiful in brain and lungs. Various names, such as cephalin, thrombokinase, cytozyme, tissue extract and platelet factor, have been applied to this substance. Should it be definitely proved an enzyme the term "thrombokinase" would be the correct one.

In order to convert prothrombin to thrombin the presence of calcium is necessary. It is not necessary in the conversion of fibrinogen to fibrin. Its mode of action is uncertain but it appears to help in the lysis of platelets. A possible explanation is that by altering the osmotic pressure in the platelet cell calcium causes absorption of water and disruption of the cell wall.

In summary, then, the coagulative process is thought to occur in two steps.

1. Calcium + thrombokinase + prothrombin = thrombin
2. Thrombin + fibrinogen = fibrin

Eagles expressed the opinion [41] that the most probable working hypothesis regarding the conversion of prothrombin to thrombin is that calcium and thromboplastin together constitute an enzyme system which, like trypsin and certain proteolytic snake venoms, activates prothrombin to thrombin.

Despite a large literature the chemical nature of antithrombin, the medium whereby thrombin is inactivated, is entirely unknown. It is an open question whether or not the relatively weak antithrombin activity of normal plasma is due to the presence of correspondingly small amounts of heparin or to some wholly unrelated factor. It is, however, clear that under physiological conditions the antithrombic activity of circulating blood or plasma is not sufficiently pronounced to prevent coagulation. Some other factor must contribute to the stability of circulating blood. The most plausible suggestion as to why circulating blood fails to clot is that the thromboplastin in the circulating blood is present in an inactive form and that it becomes available in shed blood through either the disintegration of the platelets or the activation of dissolved plasma factor by contact with a foreign surface. It is an open question whether or not as a second line of defense heparin may not be present in sufficient concentration to counteract the effect of such small amounts of active thromboplastin as may be liberated in vivo.

The possibility must be considered, however, that the body's true defense may be some substance or factor not envisaged in any of the theories previously discussed.

By other investigators [49] albumin is thought to be the normal antithrombin of the blood, although it does not become an anticoagulant until combined with heparin.

Since fibrinogen has a greater affinity for thrombin than for albumin no appreciable neutralization of thrombin occurs until all the fibrinogen is converted to fibrin. By adding heparin to albumin the affinity of the latter for thrombin is so increased that thrombin will combine with the heparin-albumin complex before it can react with fibrinogen.

The clinical results of deficiencies in these basic factors are known to some extent.

A decrease in prothrombin may be present through lack of intake or utilization of vitamin K, because of hepatic disease or from less common causes. The large physiologic excess of this constituent has been noted; this excess, together with the fact that a series of patients received vitamin K without a decrease in hemorrhage, rule out a decrease in prothrombin as a likely cause of postoperative hemorrhage after cataract extraction.

Insufficiency of fibrinogen is uncommon, but it occurs in patients with extreme nutritional deficiency, such as that found with pernicious anemia, scurvy, pellagra and leukemia. It is not likely to be a contributing element in cases of cataract such as those under consideration.

Thromboplastin deficiency may occur in association with thrombocytopenic purpura, in which the platelets are decreased in number, or hemophilia, in which their resistance is thought to be increased. No cases of such deficiency were known to be included in this series.

Regarding a calcium deficiency Quick [42] stated that no clinical or experimental hemorrhagic condition is known which can be attributed to changes in the calcium ion concentration. He stated that it is doubtful that even the extreme variation in concentration which occurs pathologically can influence clotting. Further, he cited a case of Ravdin, Riegel and Morrison [50] in which a serum calcium level of 4.6 mg. per hundred cubic centimeters occurred in a patient with parathyroid tetany while the coagulation time remained normal. In vitro, the calcium concentration can be varied rather widely without influencing the rate of coagulation.

The usual clinical tests [51] employed to estimate hemorrhagic tendencies are gross and inaccurate. Those most commonly used are

49. Quick, A. J.: The Normal Antithrombin of the Blood and Its Relation to Heparin, Am. J. Physiol. **123**:712, 1938.

50. Ravdin, I. S.; Riegel, C., and Morrison, J. L.: Coagulation of Blood: Comparative Values of Calcium and Glucose as Agents for Decreasing Clotting Time, Ann. Surg. **91**:801, 1930.

51. Quick, A. J.: Diagnosis of Hemophilia, Am. J. M. Sc. **201**:469, 1941.

determination of the clotting time (Lee and White's method), the bleeding time (Duke's method) and the clot retraction time. The clotting time, normally five to ten minutes, is usually estimated by noting the length of time it takes a sample of blood to clot in an inverted test tube of standard dimensions. The reaction is a complex one involving at least five factors, fibrinogen concentration, prothrombin concentration, platelet count, calcium content and antithrombic activity, each of which may conceivably influence the result obtained. In addition, because most of these substances are present in large physiologic excess, there may be a serious defect in one or more of the factors without an abnormal clotting time. Bleeding from one to three minutes normally occurs from a sharp stab wound in the skin. Interpretation of a prolonged time is difficult. In addition to the points noted, the bleeding time is affected by the vascularity and the vascular tonus of the skin, by the amount of tissue juices which may mix with the blood and by the external temperature.

The many suggestions which have been offered for the control of hemorrhage in general and of postoperative hemorrhage following cataract extraction in particular speak for their own inadequacy.

Administration of calcium is frequently suggested,[52] but, as pointed out by Quick, there is no logical reason for its use.

The use of vitamins C and K is undoubtedly indicated in cases in which the plasma ascorbic acid and prothrombin are unduly low, but in the present series such selected cases were few and did not account for any considerable proportion of cases of hemorrhage.

The use of gelatin,[53] histidine,[54] horse serum [10] and high protein diets [54a] would seem to be based on a hypothetic deficiency in serum protein which has not been demonstrated. A deficiency in serum protein has been shown to be a cause of disruption of abdominal wounds,[55] and

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52. Goar, E. L.: Management of the Complications of Intraocular Surgery, Am. J. Surg. **42**:62, 1938. Vail.[1m] Wright.[1r]

53. (*a*) Tainter, M. L., and Throndsen, A. H.: Hemostatic Effects of Administration of Calcium, Viosterol, Styptisate and Ceanothyn by Mouth, J. Am. Dent. A. **25**:638, 1938. (*b*) Tainter, M. L.; Throndsen, A. H., and Richardson, A. P.: Alleged Hemostatic Action of Gelatin, Coagulin, Fibrogen and Histidine Administered by Mouth, ibid. **26**:420, 1939.

54. (*a*) Kugelmass, I. N.: "Bleeding" and "Clotting" Diets, M. Clin. North America **19**:989, 1935. Tainter and Throndsen.[53a] Tainter, Throndsen and Richardson.[53b]

55. Rhoads, J. E.; Fliegelman, M. T., and Panzer, L. M.: The Mechanism of Delayed Wound Healing in the Presence of Hypoproteinemia, J. A. M. A. **118**:21 (Jan. 3) 1942. Whipple, A. O., and Elliott, R. H. E., Jr.: The Repair of Abdominal Incisions, Ann. Surg. **108**:741, 1938. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **38**:500 (March) 1938.

it is possible that it may have some bearing on the healing of limbal wounds. No experimental work has appeared on this subject.

The subcutaneous injection of solution of posterior pituitary and ergot [56] and of epinephrine hydrochloride [57] has been said to prevent or stop bleeding after cataract extraction. Sollmann [58] stated that as ordinarily used ergot does not affect the blood pressure or vessels and that its use for hemorrhage other than postpartum is irrational. In large doses it injures capillary endothelium and so produces thrombosis and gangrene but does not cause vasoconstriction. Epinephrine, as is well known, controls capillary bleeding effectively when applied locally but has little effect on arterial or venous bleeding. When its action has disappeared secondary hemorrhage frequently occurs if the clot fails to adhere to the dilating blood vessel. Spanyol [59] has described a case of severe postoperative hemorrhage in which he removed the clot and instilled 0.5 cc. of 1:1,000 epinephrine hydrochloride with a lacrimal irrigator directly into the anterior chamber, a procedure said to have produced immediate and permanent cessation of bleeding. Use of this drug internally is apt to be unsuccessful if not definitely harmful, the rise in blood pressure overcoming the local vasoconstriction. Coagulability of blood is not influenced by epinephrine. Solution of posterior pituitary injected parenterally has disadvantages somewhat similar to those of epinephrine.

Thromboplastic substances have been used by a number of authors, who have given conflicting reports. Black [60] reported a case of severe bleeding after an intraocular operation which was controlled by injection of thromboplastin and recurred after use of the drug was stopped. Vail used thromboplastin in 1 case without effect. Busacca [61] has used for some years, with apparent success, a proprietary coagulant made from blood platelets of the horse. Yet Aggeler and Lucia,[45] investigating a number of commercial thromboplastins, found that solutions for hypo-

56. Ziegler, S. L.: The Problem of Choroidal Hemorrhage in Cataract Extraction, in Contributions to Ophthalmic Science, Dedicated to Dr. Edward Jackson, Menasha, Wis., George Banta Publishing Company, 1926.

57. Thiellez, L.: Un traitement des hémorrhagies expulsives, Bull. et mém. Soc. franç. d'opht. **35**:406, 1922. Berens and Bogart.[10]

58. Sollmann, T.: Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 436.

59. Spanyol, V.: Beseitigung postoperativer Blutergüsse der vorderen Kammer und ein Versuch zur Vereitelung neuer Blutaustritte in dieselbe, Klin. Monatsbl. f. Augenh. **96**:670, 1936.

60. Black, M.: Hemorrhage After Cataract Operation, Am. J. Ophth. **7**:539, 1924.

61. Busacca, A.: Advantages of the Use of Coagulants in Ocular Operations, Especially in Extraction of Cataract and in Plastic Operations, Arch. Ophth. **20**:406 (Sept.) 1938.

dermic use were uniformly inactive. It was their feeling that it was not yet (1940) possible to refine or concentrate the active components of these solutions. For intraocular operations Busacca has injected 20 cc. of his coagulant into the abdominal subcutaneous tissue. Within two hours the effect of the drug is manifest, and it continues for several more hours. He has noted that after this procedure when blood appears in the anterior chamber it coagulates more quickly and can be easily removed with a forceps. He also has said that the tenacity of the coagulum makes the conjunctival flap more solid and promotes restoration of the anterior chamber. Similarly, in plastic procedures the graft or flap will adhere better. For plastic operations and enucleation Busacca has stated a preference for the powder placed directly on the operative field. Injection of thromboplastin was abandoned in plastic procedures after the appearance of slough. In this connection it might be noted that other authors have reported severe systemic reactions, including fever, rapid pulse, precordial pain, vomiting, clonic contractions of sets of muscles and convulsions, and at least 2 deaths have occurred after the intravenous use of thromboplastin. Gold [62] in 1932 after reviewing the literature concluded that the so-called thromboplastic agents are useless. Bethea [63] reached a similar conclusion in 1934. Gold also surveyed ten New York hospitals and reported that all of them had at one time used thromboplastic agents and had discarded them as useless if not dangerous. Should such a substance be potent the possibility of intravenous or intramuscular clotting would be great.

Tainter and associates [53] in a small but controlled series investigated the worth of certain coagulants which had been widely used in dentistry for undue bleeding after extractions of teeth. These included calcium gluconate both with and without viosterol, gelatin, histidine, thromboplastic substance and several proprietary drugs. The authors concluded that dentists should stop using systemic measures to prevent hemorrhage and should rely entirely on local means.

In 1936 Graves and Kickham [64] reported the use of congo red intravenously for the control of hematuria and as a prophylactic after prostatectomy. In 1930 Wedekind had accidentally discovered that it has a beneficial effect in pulmonary hemorrhage. It was believed that congo red accelerates clotting by activating prothrombin and by increasing platelets and thrombokinase. No reports have appeared in the ophthalmic literature.

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62. Gold, H.: Control of Hemorrhage by Thromboplastic Agents, Internat. Clin. **2**:293, 1932; **3**:237, 1932.

63. Bethea, O. W.: Thromboplastic Agents in Clinical Medicine, Internat. M. Digest **25**:375, 1934.

64. Graves, R. C., and Kickham, C. J. E.: Congo Red for the Control of Bleeding, New England J. Med. **214**:782, 1936.

Lately extracts have been made from certain plants which have been found to accelerate the coagulation of blood. These contain certain dicarboxylic acids, of which oxalic acid is the principal one.[65] The action of these extracts is surprising, since similar dibasic acids are used for the opposite purpose in transfusions. The mechanism for the reversed action of oxalic acid in vitro and in vivo is not clear. It seems to act as a catalyzer and adds to the function of tissue juices, platelets and calcium in the formation of thrombin. The drug is said to have been used successfully in the treatment of hematemesis, gastric ulcer, jaundice, hemoptysis, hematuria, epistaxis, hemophilia and melena neonatorum and has been reputedly used in several thousand cases without toxic symptoms. No reports on ophthalmic application have appeared.

Nicotinic acid has been found[66] to promote blood coagulation in patients with chronic brucellosis and also seems useful in hemorrhagic states resulting from toxic or infectious causes. It is assumed that nicotinic acid corrects some fundamental deficiency in the organism and has no direct effect on the clotting mechanism.

Recently[67] a globulin fraction of rabbit's blood has been shown to have a strong thrombic activity and to be of value by local application in controlling hemorrhage from small wounds. This it does by the immediate precipitation of fibrin. Parenteral administration causes a toxic reaction, however, and may result in generalized thrombosis. Purified thrombin has also been shown by Warner, Brinkhous, Seeger and Smith[68] to be useful as a local hemostatic.

Snake venom has been advocated in the ophthalmologic literature in order to prevent not only the hemorrhage due to operative trauma

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65. Milliken, L. F.: The Use of a New Blood Coagulant in Transurethral Prostatic Resection, J. Urol. **42**:75, 1939. Steinberg, A., and Brown, W. R.: A New Concept Concerning the Mechanism of Clotting and the Control of Hemorrhage, Am. J. Physiol. **126**:638, 1939. Schumann, E. A.: Newer Concepts of Blood Coagulation and the Control of Hemorrhage, Am. J. Obst. & Gynec. **38**: 1002, 1939. Foster, R. H. K.: On the Role of Oxalic Acid in Blood Clotting, Proc. Soc. Exper. Biol. & Med. **44**:136, 1940. Martin, G. J.: The Mechanics of Action of Dicarboxylic Acids in Blood Coagulation, Am. J. Physiol. **130**:574, 1940.

66. Calder, R. M., and Kerby, G.: The Effect of Nicotinic Acid on Blood Coagulation, Am. J. M. Sc. **200**:590, 1940.

67. Parfentjev, I. A.: A Globulin Fraction in Rabbit's Plasma Possessing Strong Clotting Property, Am. J. M. Sc. **202**:578, 1941. Taylor, F. H. L.; Lozner, E. L., and Adams, M. A.: The Thrombic Activity of a Globulin Fraction Derived from Rabbit Plasma, ibid. **202**:585, 1941. Lozner, E. L.; MacDonald, H.; Finland, M., and Taylor, F. H. L.: The Use of Rabbit Thrombin as a Local Hemostatic, ibid. **202**:593, 1941.

68. Warner, E. D.; Brinkhous, K. M.; Seeger, W. H., and Smith, H. P.: Further Experience with the Use of Thrombin as a Hemostatic Agent, Proc. Soc. Exper. Biol. & Med. **41**:655, 1939.

but that due to systemic disease.[69] Nearly all venoms derived from serpents for therapeutic use contain hemolysin, hemorrhagin, proteolysin and neurotoxin in varying amounts.[70]

Usually one of these elements predominates in an individual venom. In 1937 Eagle,[71] during an investigation of the coagulating mechanism of the blood, found that nine of seventeen venoms tested were capable of coagulating citrated blood or plasma. Seven of these converted fibrinogen directly to fibrin. Three also converted prothrombin to thrombin without the addition of calcium or platelets. Moccasin venom had no direct coagulating power. Its effect,[72] if any, is therefore thought to be due to some undetermined effect on capillary walls. As late as 1940 the Council on Pharmacy and Chemistry of the American Medical Association [70a] reviewed the evidence for the use of moccasin snake venom and concluded that as its usefulness and limitations had not been established the drug should not be included in "New and Nonofficial Remedies." Its reputed value in ophthalmic surgery should be viewed critically until further evidence has been presented.

The application of any of these therapeutic means to prevent hemorrhage in the immediate problem under discussion, that is, bleeding following cataract extraction, does not appear to offer much promise. It is possible that the use locally of such styptics as purified thrombin, rabbit globulin or some of the snake venoms may be of assistance in keeping the operative field free of blood, but it does not appear likely to lessen the incidence of the fourth to fifth day hemorrhage which is so frequently associated with cataract operations.

Other systemic measures have been suggested, including elimination of foci of infection [10]; control of blood pressure, diabetes and syphilis, and phlebotomy when hypertension exists.[73] Some observers [74] have stated the belief that a paracentesis and evacuation of blood from the

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69. Rosenfeld, S., and Lenke, S. E.: Tiger Snake Venom for the Treatment of Accessible Hemorrhage, Am. J. M. Sc. **190**:779, 1935. Swett, W. F.: Snake Venom: Its Use in Postoperative Hemorrhage of the Eye, California & West. Med. **48**:173, 1938. Alvaro, M. E.: Snake Venom in Ophthalmology, Am. J. Ophth. **22**:1130, 1939.

70. (*a*) Snake Venom Solution (Moccasin) Not Acceptable for New and Nonofficial Remedies, report of the Council on Pharmacy and Chemistry, J. A. M. A. **114**:2218 (June 1) 1940. (*b*) Cobra Venom Solution, preliminary report of the Council on Pharmacy and Chemistry, ibid. **115**:1196 (Oct. 5) 1940.

71. Eagle, H.: The Coagulation of Blood by Snake Venom and Its Physiologic Significance, J. Exper. Med. **65**:613, 1937.

72. Snake Venom, report of the Council on Pharmacy and Chemistry, J. A. M. A. **104**:1073 (March 30) 1935.

73. Vail.[1m] Philps.[1n] Berens and Bogart.[1o] Wright.[1r] Focosi.[8a] Kirby.[8b] Gifford.[9a]

74. Vail.[1m] Davis.[1q]

anterior chamber will prevent recurrent hemorrhage. None of these measures has proved to be of real value.

SUMMARY

1. Of 453 consecutive cataract operations, postoperative hemorrhage appeared after 95, an incidence of about 20 per cent.

2. Age, time of year, systolic and diastolic blood pressure, the presence of diabetes or syphilis and elevated intraocular pressure were not found to be related to postoperative hemorrhage.

3. The type of operation used, presence or absence of retrobulbar injection, type of suturing and skill of the individual surgeon were not found to be significant.

4. The performance of an iridectomy at the time of extraction increased the chance of subsequent hemorrhage by about 20 per cent.

5. Determinations of the plasma ascorbic acid and tests for capillary fragility are not reliable in predetermining hemorrhage. Vitamin C subnutrition is not a common cause of hemorrhage after cataract extraction.

6. Deficiency in plasma prothrombin associated with lack of vitamin K is not an important cause of hemorrhage after cataract extraction.

7. Systemic measures, such as the use of snake venom, calcium, thromboplastic substances, protein diets and various proprietary drugs, do not appear useful as preventive agents. Local application of certain substances may prove to be of some value.

The vitamin C determinations were made by Mr. Henry S. Bloch, of the Department of Ophthalmology. The prothrombin determinations were made by Miss Josephine Galloway, of the Department of Surgery. The vitamin K used was supplied by E. R. Squibb & Sons.

30 West Fifty-Ninth Street.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Prize Offered for Contribution on Glaucoma.—A prize of $250 is offered for the most valuable original contribution adding to existing knowledge about the diagnosis of early glaucoma during 1943. The award will be made through the National Society for the Prevention of Blindness with the guidance of an ophthalmologic committee composed of Drs. Arnold Knapp, Manuel Uribe Troncoso and Mark J. Schoenberg. Papers may be presented by any research worker, student in ophthalmology or ophthalmologist of the Western hemisphere and may be written in English, French, German, Italian, Spanish or Portuguese. If written in one of the last four languages, the paper should be accompanied by a translation in English. Papers should be in the office of the National Society for the Prevention of Blindness, 1790 Broadway, New York, by Sept. 15, 1943.

Correspondence

PARALLACTIC ANGLE IN BINOCULAR DEPTH PERCEPTION

To the Editor:—The article by Dr. Joseph I. Pascal "Parallactic Angle in Binocular Depth Perception" (ARCH. OPHTH. **28:** 258 [Aug.] 1942) is interesting because it shows renewed attention to problems relating to military service. Perception of depth is an important factor, especially in so far as flying is concerned.

The explanation given in the article, however, is not an explanation of the parallactic angle. It is a complicated explanation of the angle of convergence, which is another of the factors involved in depth perception. This explanation when reduced to its simplest form resolves itself into the fact that there is a different angle of convergence between the two eyes when first one object is fixed by binocular vision and then another, which is either nearer or farther away. This is the well known factor of convergence. The ingenious explanation of dextroversion and levoversion with convergence and divergence stimuli only serves to complicate the picture unnecessarily.

The perception of depth is based on a number of factors. These can be divided into the basic factors, or the factors inherent in the individual which enable him to distinguish depth, and the adjunctive factors.

The adjunctive factors will be considered first; they consist of data that can be obtained from the environment and they provide hints as to relative distances involved.

These factors are

(*a*) Size of retinal image

(*b*) Motion parallax

(*c*) Terrestrial association

- (1) Linear perspective
- (2) Overlapping contours
- (3) Light reflection and shadows
- (4) Aerial perspective

The basic factors which give the individual his inherent ability to perceive depth are as follows:

(*a*) Physiologic diplopia, the well known phenomenon in which when an object is fixed by binocular vision other objects, nearer or farther away, are seen double

(*b*) Accommodation, in which the amount of accommodation used to focus an image clearly is interpreted as a certain amount of distance.

(*c*) Convergence, in which the amount of convergence in use when a single object is viewed with binocular vision is interpreted in terms of a certain amount of distance

(*d*) Binocular parallax, which will be discussed hereafter

Binocular parallax is based on the fact that the two eyes, being separated by the interpupillary distance, get different views of the same object or objects and thereby get an impression of relief, solidity and depth. This factor may operate to give an impression of depth of a single object or of a difference in depth of two objects. It is operative only when the object or objects can be seen without moving the eyes. If the relative distance to two objects is to be determined when they cannot be viewed simultaneously, binocular parallax can be used only by determining the distance of each object separately in relation to a common background and thereby getting an impression of the relative depth of the two individual objects.

Figure 1 illustrates the parallactic angle which is operative in perception of the depth of a single solid object. It will be noted that

Fig. 1.—Parallactic angle (single solid object). Dissimilar images received in each eye give the impression of depth. Surface *A-B* subtends a larger visual angle in the right than in the left eye. The parallactic angle equals angle *ARB* minus angle *ALB*.

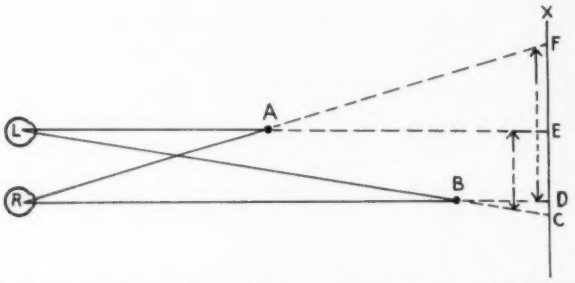

Fig. 2.—Parallactic angle (two objects). The portion of the background visible between objects *A* and *B* is larger in the right eye (space *D-F*) and subtends the visual angle *ARB*. The portion of the background visible between *A* and *B* by the left eye is smaller (space *C-E*) and subtends the angle *ALB*. The parallactic angle equals angle *ARB* minus angle *ALB*.

the surface *A-B* is visible to both eyes but that it subtends a much larger visual angle in the right eye (angle *ARB*) than it does in the left eye (angle *ALB*). The dissimilarity of retinal images gives an impression of depth. The difference between the angle *ARB* and the angle *ALB* is the parallactic angle involved.

When the difference in depth between two separate objects is to be determined, the same general situation prevails. Each eye obtains a slightly different view of each of the two objects, and the images of these two objects fall on slightly dissimilar portions of the retina. This fact can be most easily illustrated by using as the image the

amount of background which is visible between the two objects *A* and *B* in figure 2. It will be noted that the right eye will see the amount of background *D-F* between the two objects *A* and *B*, whereas the left eye will see the portion *D-E* between the same two objects. The portion of the background *D-F* subtends the visual angle *ARB*, which is larger than the visual angle *ALB*, subtended by the portion of the background *C-E*. The parallactic angle in this instance is the difference between the angle *ARB* and the angle *ALB*.

Dr. Pascal has stated correctly that the maximum size of the parallactic angle which qualifies a person for flying duty is ten to twelve seconds of arc and represents a maximum linear displacement of 30 to 35 mm. at 6 meters. He also called attention to the fact that the exact angle varies with the interpupillary distance and will be greater when this distance is larger.

V. A. Byrnes, Lieutenant Colonel, M. C., U. S. A.

Obituaries

OSIP RAPHAEL LOURIE
1873-1941

Osip Raphael Lourie, uprooted by the Russian revolution, settled in Boston in 1922. He was then 49 years old and had attained eminence as a practitioner and teacher in ophthalmology in Kiev, Russia. Although he was practically a stranger when he came to Boston and was without material resources, the high esteem in which he was held in his native land followed him and quickly won him a place in this city. He built up a fine, devoted clientele and used most of his income, after bringing over his family, in helping many relatives and friends, far and near. No appeal to him was unanswered.

He was a genial, happy, cultured gentleman, deeply sentimental and of dignified bearing. He was the life of any gathering, with ready humor, a contagious laugh and ease at the piano.

He was a liberal. He read widely and thought deeply and fought for the truth even if it meant loss of favor. He could express himself vigorously with the written and the spoken word, as evidenced by his articles on focal infection (ARCH. OPHTH. **5:** 893 [June] 1931; **8:** 24 [July] 1932; **9:** 918 [June] 1933) and on total ablation of the thyroid.

His ever youthful, spontaneous enthusiasm was a stimulus to his many friends, and his memory will remain warm with them.

He died a year ago, Oct. 27, 1941.

HYMAN MORRISON, M.D.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Conjunctiva

PRIMARY DIPHTHERITIC CONJUNCTIVITIS IN THE INFANT. B. V. RE and V. MUHLMANN, Arch. de oftal. de Buenos Aires **16:** 261 (May) 1941.

Diphtheria in the nursing infant, which although rare is not exceptional, has distinguishing features.

After a brief reference to the usual localizations, of which the nasal is the most frequent, the authors detail a case of primary diphtheritic conjunctivitis in a nursing infant 17 days old. This is the second case reported in Argentina. The diagnosis was confirmed by the finding of Löffler's bacillus in the exudate and the corresponding objective and subjective symptoms, with absence of invasion of the nasal and pharyngeal mucosa. Complete recovery was obtained with the use of antidiphtheritic serum.

The frequency, etiology, symptomatology, treatment, pathology and pathogenesis in general are discussed. C. E. FINLAY.

EPITHELIAL CONJUNCTIVAL PLAQUES. J. MALBRÁN and B. TOSI, Arch. de oftal. de Buenos Aires **16:** 484 (Sept.) 1941.

A case is reported of an epithelial plaque with a papillomatous structure occupying the internal palpebral fissure and subject to frequent recurrences.

The extensive literature of similar lesions, described under different captions (tyloma, conjunctival cornification, keratosis and callosity) is reviewed, and a minute histologic report is given. C. E. FINLAY.

EVALUATION OF WEIL-FELIX REACTION IN TRACHOMA: REPORT OF A CASE. W. ROHRSCHNEIDER, Klin. Monatsbl. f. Augenh. **104:** 609 (May) 1940.

Recent research on the origin of trachoma seems to support the view that the disease is caused by Rickettsia and that certain correlations exist with spotted fever, one of the best established forms of rickettsiosis. Rohrschneider presents a description of the Weil-Felix reaction, established in 1916; favorable and unfavorable views of a number of writers, and several tables. He adds statistics on trachoma in Yugoslavia, Morocco and Italy and reports comparative research done in Königsberg and Frankfort on the Main, Germany, on two Proteus X 19 strains in trachoma and spotted fever. He discusses the serologic analogies between these two diseases.

The author advises consideration of the sources of errors in the Weil-Felix method as used for the diagnosis of glaucoma. The reaction may be considered positive only if agglutination occurs in a dilution of more

than 1 : 100 after the culture has remained in the incubator for two hours. Readings after twenty-four hours may result in intercurrent unspecific reactions. The patients under examination came from a district infested with spotted fever. The results were fairly equal in these patients and in control subjects. Actually, positive reactions in a case of trachoma may be due to a previous infection with spotted fever or with proteus baccilli. A case in point is reported. Agglutination tests with a proteus strain derived from the conjunctival secretion of a trachomatous patient gave negative results in cases of trachoma. In the author's opinion neither his own results nor those of other writers furnish proof that the Weil-Felix reaction is of neither practical nor theoretic importance in the diagnosis of trachoma.

K. L. STOLL.

Cornea and Sclera

FAMILIAL DYSTROPHY OF CORNEA: REPORT OF A CASE OF PECULIAR CENTRAL FLAKY AND PERIPHERAL LATTICE-SHAPED OPACITIES. A. PILLAT, Klin. Monatsbl. f. Augenh. **104:** 571 (May) 1940.

Pillat accepts Bückler's division of familial dystrophy of the cornea into three types. He reports a case in which the patient in his opinion represented a fourth type. Central and peripheral corneal changes were present. The patient was a woman aged 56. One sister showed similar changes; two other sisters did not. Her father, his brother and their father were probably afflicted, judging by the family history. The exhaustive report has several illustrations, among them three slit lamp views in color. Two separate pathologic zones were observed in the corneas, a central and a peripheral zone.

Flaky corneal opacities of varying size were noted in the central zone. They measured less than 0.5 mm., were located in the deeper and central layers of the cornea and presented a lenticular shape on cross section. The opacities were irregularly scattered and were surrounded by perfectly clear corneal tissue. No latticed or annular arrangements were seen.

The peripheral zone, adjoining closely the circumference of the limbus, contained numerous glassy lines. They were closely packed and about 0.75 mm. in size, ran in a radial direction and crossed one another occasionally. These glassy lines could be observed only with the slit lamp in indirect light. The corneal nerves and the sensitivity of the cornea were normal; corneal vessels were absent. The pathologic changes described occurred in three generations; they were dominantly hereditary. Considerable deficiency of vision occurred only at a late age. The central corneal opacities were supposed to be hyaline flakes derived directly from the albumin of the corneal lamellas wherever they developed. It was impossible to explain by clinical observation the nature of the glassy lines near the limbus; they resembled the latticed lines in latticed dystrophy of the cornea. Notwithstanding the similarity between the central flaky opacities and the opacities of granular corneal dystrophy, they differ in this respect: In Pillat's case the opacities occurred more in the deeper layers, they were irregularly scattered and the periphery of the cornea was involved. In Pillat's opinion these symptoms classify the case as an instance of a special type of familial corneal dystrophy.

K. L. STOLL.

OBSERVATIONS ON CORNEAL TRANSPLATATION: REPORT OF A NEW TECHNIC AND OF CASES. J. IMRE, Klin. Monatsbl. f. Augenh. **104**: 589 (May) 1940.

Imre has been practicing a new method of transplantation of the cornea for six years. He forms a lateral corneal flap at the temporal side of the eyeball. A flap of this description cannot move when the dressing is changed. It can readily be pulled across the entire cornea, because the lateral part of the fornix is very shallow. The incision measuring 10 mm. is done through the superficial layers of the conjunctiva with avoidance of the deeper layers. An especially broad conjunctival bridge is formed in the presence of conjunctival scars. Corneal sutures for fixation of the transplant are advisable only in cases in which the available conjunctiva is insufficient to cover the transplant. Two sutures for fixation of the flap are laid loosely before the transplantation and tied after the transplant is in position.

Imre prefers von Hippel's trephine; he avoids the hand trephine because it requires the use of scissors and forceps. He used the electric trephine only once, as it endangers iris and lens.

After experimenting on 19 blind patients who were unable to recognize objects, Imre performed 53 transplantations. He obtained lasting and considerable improvement of vision in 23 cases. Good results were obtained in 11 cases of corneal opacification caused by parenchymatous keratitis, in 1 of which this condition was combined with central necrosis of the cornea and applanation. The cornea regained its normal curvature after the operation. In several cases of leukoma adhaerens and in 2 cases of lime burns there were good results, although in such cases the circumstances are usually unfavorable. In a case of trachomatous pannus and cicatricial shrinkage of the fornices, a good result was obtained with transplantation, and this was not affected by extraction of a senile cataract two months later. Injury by cement had caused a leukoma involving almost the entire cornea. The leukoma had been well tattooed by another oculist. Lacteal cataract was noted by Imre after removal of the corneal flap. He removed the lens through the opening of the transplant. Vision of 5/10 was recorded when the patient was discharged from the hospital and full vision a year later. Two further cases are reported, in which not only did the transplant remain clear but the surrounding cornea cleared gradually. The comparatively low percentage of good results was due to the fact that many cases were so-called hopeless cases. Imre repeats his previously expressed opinion that opacities resulting from parenchymatous keratitis, lymphatic keratitis and trachomatous pannus are favorable for transplantation after his method. Adhesions between the flap and the edge of the transplant occurred in some cases but were readily separated with a spatula. All transplants were taken from living eyes. Corneas of aged persons, including aged glaucomatous patients, were less apt to cloud up or swell. Eyes with intraocular tumors were suitable, but far less so were eyes with penetrating wounds.

K. L. STOLL.

Experimental Pathology

EXPERIMENTAL RESEARCH ON RABBITS: DISK-SHAPED AND RING-SHAPED PROGRESSIVE LIPOID INFILTRATION OF CORNEA. M. VERSÉ, Klin. Monatsbl. f. Augenh. **104:** 553 (May) 1940.

Experiments on lipoid degeneration in the rabbit are difficult because this animal has a comparatively short span of life and because it cannot stand fatty nourishment in doses sufficient to produce the lipoid changes.

One rabbit of a series offered favorable conditions. Corneal changes were observed in the right eye after three months' feeding with cholesterol and linseed oil. Different changes appeared in the left eye a few months later. The cholesterol content in the blood had increased considerably. Adaptation to the large cholesterol content in the blood was evident by greater elimination and by a gain of weight from 2,100 Gm. to 2,950 Gm. The disk-shaped opacity of the right cornea showed histologically profuse infiltration with round cells, strongly filled blood vessels, foam cells, coarse fat globules which stained well with sudan and numerous tightly packed double-refracting crystals of cholesterol substances. The entire cornea was thickened and resembled an ectasia or staphyloma. The arcus was small, but large deposits were found in the sclera and choroid of the posterior segment of the eyeball and adjacent to the ciliary body. The arcus in the left eye was much broadened but free from lymphocytes, whereas narrow vessels and tubular pseudoxanthoma cells were evident between the lamellas. A layer resembling pannus appeared beneath the epithelium of the cornea, and Bowman's membrane was barely noticeable. Color plates illustrate the condition. Exact data on feeding of the animals are recorded, references to the literature in point are presented and cases of such degeneration in man are cited.

Discussing the evidence pro and con, Versé draws these conclusions with reference to the pathologic changes in man and in other animals: The lipoid changes in the cornea are infiltration of fat occurring simultaneously with an increase of the lipoid content in the blood and receding with its decrease. The different forms of the changes depend on local conditions. A primary inflammation in the cornea will produce a correspondingly large disk-shape lipoid infiltration, with new formation of blood vessels following. The appearance of a more or less rudimentary arcus may be taken as a harmless symptom of hyperlipoidemia. An arc-shaped opacity becomes ring-shaped when the marginal deposits increase, and vascularization follows. This phenomenon occurs as a result of an increased fat intake (e. g., in arcus juvenilis); of a decreased intake connected with senile changes in the tissues (arcus lipoides senilis); of local disturbances of the circulation (arcus lipoides partialis). The occurrence in the same animal of primary changes in the right eye and of secondary changes in the left eye is significant. It is pathologic evidence for Rhor-Schneider's theory based on clinical observation. Versé proposes the adoption of the terms annulus and discus, respectively, lipoides progrediens in connection with the accepted term "arcus lipoides corneae."

L. K. STOLL.

General

HOSPITAL LIGHTING FOR PROTECTION IN WAR TIME. C. E. FERREE and G. RAND, Brit. J. Ophth. **26:** 310 (July) 1942.

Ferree and Rand have devised a fixture which combines all the advantages of direct and of indirect lighting and at the same time corrects as far as possible their faults and deficiencies.

The lighting given by this fixture is a new type, which may be called louvered direct-indirect. Some of the results achieved are a better balanced distribution of light than is obtained with either direct or indirect lighting; complete elimination of all glare and high brightness from the source of light, the fixture and every part of the field of view; a high degree of diffuseness of light; confinement of the light to the room illuminated as far as is possible with any fixture construction that would be acceptable in good hospital lighting.

The article is illustrated.

W. ZENTMAYER.

General Diseases

ORAL SEPSIS IN RELATION TO OPHTHALMOLOGY. H. T. ROPER-HALL, Brit. J. Ophth. **26:** 141 (April) 1942.

This is the Middlemore Lecture of 1941. The subject as viewed by a dental surgeon is of interest to the ophthalmologist:

"Hunter originated the term and thus described it (1930):

"'"Dental Sepsis" seemed to me to place the whole responsibility of dealing with the subject upon the dental surgeon, whereas my whole thesis was that the first responsibility for recognising and appraising the possible importance of the sepsis presented in the mouths of his patients, rested, in the first instance, upon the doctor in charge of the case. It was to emphasise this fact that I devised the alternative name of "oral sepsis."'

"The degree of oral sepsis cannot be expressed in terms of 'infected teeth' only; it must have regard to all the other conditions present, such as gingivitis, tartar deposit, ulceration and pocketing, pyorrhoea, periodontitis and osteitis shown by recession of gums or looseness of teeth, or by thickening of alveolar margins, and conditions revealed by radiographs of apical abscesses and granulomata, buried roots, or impacted or unerupted teeth.

"Oral sepsis far exceeds that of any other form of focal infection, and the amount and character of the systemic effects which may be produced by any particular degree of dental sepsis depend upon the character and virulence of the particular infection that happens to be present, and also upon the degree of resistance the individual patient may be capable of offering."

Transmission of sepsis may be by direct extension, lymphatic and venous extension, extension through the general blood supply, swallowing the pus and its effect when absorbed from the bowel and neuropathic transmission of antidromic impulses as a result of septic irritation of nerve endings.

"Ill-fitting crowns and bridge work causing stress on the teeth or gums, ill-fitting dentures and dentures which have outlived their allotted

time are also causes of sepsis; vulcanite, naturally porous, becomes in time the seat of bacterial activity, causing inflammation of the mucous membrane of the mouth, formerly called 'denture sore mouth,' and the septic material is 'sucked' across the plate by capillary attraction and to other teeth not previously affected.

"Dentures are often worn too long, causing first a mucous membrane which is chronically inflamed, and a ready means of absorption of toxic products, and secondly 'buccal' ulcers, so slow and chronic that often the patient is unaware of their presence, which are most resistant to treatment.

"The 'pumping action,' of dentures and loose teeth causes infected lymph from the mucous or periodontal membranes to be forced into the blood-stream, resulting in transient bacteraemia at each meal-time.

"Dentures worn too long cause alterations within the temporo-mandibular joint often followed by pain of 'trigeminal' type."

Experience of oral sepsis in ophthalmic conditions strengthens the author's opinion that practically all patients are benefited by prompt and early oral treatment. He recommends that each ophthalmic hospital have a dental surgeon and that the opinion of a dentist be obtained in all cases at the earliest possible moment after admission. The attendance of dental surgeons during the usual visiting periods of other members of the staff would allow opportunities for comparison and consultation, to the ultimate benefit of patients.

W. ZENTMAYER.

Hygiene, Sociology, Education and History

SYMPOSIUM—INDUSTRIAL OPHTHALMOLOGY IN THE WAR EFFORT: THE NEED FOR A MORE REALISTIC OPHTHALMIC SERVICE IN INDUSTRY. A. C. SNELL, New York State J. Med. **42:** 1435 (Aug. 1) 1942.

Snell defines good vision as "that degree of visual functional ability which is adequate to perform the visual task presented." For industrial demands on vision, eyes fall into two general groups. The first comprises those eyes that have, or can be made to have, normal function, or "good vision," for all the complex acts of vision. The second comprises those eyes that do not have, and cannot be made to attain, this high standard of functional ability. The author's investigations reveal that in many fields of ophthalmology there is inadequate service today. The responsibility for better care of the eyes rests primarily on three groups of persons: first, on management; second, on labor or its representatives, and, third, on ophthalmologists in cooperation with the rest of the medical profession.

W. ZENTMAYER.

STEREOSCOPIC VISION IN INDUSTRY. M. DAVIDSON, New York State J. Med. **42:** 1441 (Aug. 1) 1942.

Davidson discusses several devices that have been used for the measurement of stereoscopic acuity. He points out that there are inherent errors in the measurement of stereoscopic acuity greater than those in the measurement of visual acuity, owing to the fact that stereoscopic acuity is inversely proportional to the square of the distance at which

a given depth difference is correctly perceived, while visual acuity is inversely proportional to the distance only at which it is tested. He states:

". . . in the examination of industrial workers, and for the purposes of vocational guidance, those having 20 seconds of arc may be regarded as normal, those having 20 seconds to 46 seconds as fair, and those having between 46 seconds and 120 seconds as poor in stereopsis, and those having more than 120 seconds as not possessing demonstrable binocular stereopsis. Certain occupations are already known to require superior or normal depth perception. Thus, the Committee on Standardization of Visual Requirements of Public Transportation Services Personnel of the Thirteenth International Congress of Ophthalmology recommended 'perfect' depth perception for aviators, marine officers, and public motor vehicle drivers, and 'good' depth perception for railway engineers and private car drivers. While in time of peace, the distinction between public services and private industry is warranted, in wartime industry becomes endowed with the character of a public service, and an accident in a munitions plant or an airplane factory becomes as important as a railway collision. Aside from workers in the public transportation services, those in certain other occupations obviously also require normal depth perception—such as crane operators, workers on elevated structures, machinists, carpenters, filing clerks, and cutters in the garment industry. It is quite probable that in these occupations, and many others, normal depth perception is of more importance than normal visual acuity. Normal depth perception is, moreover, compatible with low visual acuity, and normal visual acuity in both eyes does not necessarily mean normal depth perception. It may be quite unaffected by the low visual acuity. It may also improve with the correction of an error of refraction of a high degree. Three cases recently examined bear this out. . . .

"In conclusion, the prevalence of lack of binocular stereopsis, and of serious impairment of it, the existence of means of measuring it, and the obvious importance it has in the prevention of accidents and in the proper job placement of workers in the interest of national protection, should make the testing and measuring of depth perception a standard, routine practice in the examination of eyes, alongside of visual acuity testing. It is not, however, a mechanical procedure, and, until the apparatus and methods are better standardized, it cannot be relegated to lay persons unless they are trained and supervised by an ophthalmologist."

W. ZENTMAYER.

THE PROBLEM OF FAULTY STEREOPSIS IN INDUSTRY: A PRELIMINARY STUDY OF CERTAIN OPERATIONS IN THE PUBLISHING INDUSTRY. L. D. REDWAY, New York State J. Med. **42:** 1445 (Aug. 1) 1942.

The printing and publishing industry uses today millions of metal stencils for the purpose of addressing mail. These stencils, before and after use, must be checked with copy for correctness of name, address and code marks and then be sorted and filed in drawers in correct relation to the stencils lying before and behind. Filing operations of this kind involve judgment of spatial relationships, accurate correlation of hands and eyes, oculomuscular adjustment, the phenomenon of successive parallax and the interpretative faculties of experience.

The writer examined 281 employees of a publishing plant and found that 54, or 19.2 per cent, were deficient in some degree of stereopsis; of these, 8 had absolutely no demonstrable depth perception. In a second group of 375 employees, 21.4 per cent were deficient in some degree. Nine, or 2.4 per cent, had no stereopsis whatever.

W. ZENTMAYER.

INDUSTRIAL OPHTHALMOLOGY FROM THE PUBLIC HEALTH VIEWPOINT. L. GREENBURG, New York State J. Med. **42:** 1448 (Aug. 1) 1942.

"In American life today there is considerable needless loss of visual efficiency and actual loss of visual capacity. Because of the fact that these losses are to a large extent preventable, they constitute a challenge to the public health profession. . . . For this reason an organized campaign along production lines should be formulated."

The elements of this campaign might well come under five chief classifications: (1) preventive medical care, (2) ophthalmic examinations, (3) establishment of optimum seeing conditions—more adequate illumination, (4) control of accidental injuries to the eyes and (5) a mass educational campaign.

W. ZENTMAYER.

Neurology

AVIAN THIAMINE DEFICIENCY: II. PATHOLOGIC CHANGES IN THE BRAIN AND CRANIAL NERVES (ESPECIALLY THE VESTIBULAR) AND THEIR RELATION TO THE CLINICAL BEHAVIOR. R. SWANK and M. PRADOS, Arch. Neurol. & Psychiat. **47:** 97 (Jan.) 1942.

The authors summarize previous work on the clinical and pathologic manifestations of a deficiency of thiamine in pigeons before presenting their new work on lesions in the brain and cranial nerves in thiamine-deficient pigeons and correlation of these lesions with clinical observations.

They find that "the previous and the present study have shown that the predominating pathologic changes in thiamine-deficient pigeons can be varied considerably by altering the speed of thiamine depletion. In birds made acutely deficient the vestibular system suffered the first and most severe degeneration. This was followed closely by degeneration in the cerebellum and, in some cases, the optic lobes. In very chronic preparations, degeneration of peripheral proprioceptive nerve fibers appeared first and sometimes became marked before changes appeared elsewhere. Later, lesions in the cerebellum, vestibular system and optic lobes developed, the severity of changes in each system varying but conforming roughly to the order named. The oculomotor and trochlear nerves and their nuclei degenerated later. In cases of intermediate (subacute) deficiency, the pathologic course was less distinctive. Degeneration of the cerebellar systems and spinocerebellar tracts was frequently the more marked. Changes in the vestibular system were present but not so prominent, and the optic system was affected to a variable degree. The sequence of events which have been seen in the more chronically thiamine-deficient pigeons conforms in a general way to the progression of neurologic manifestations in several alcoholic patients. Ataxia and weakness of the extremities were followed by ophthalmoplegia, and

regression of symptoms in reverse order occurred when vitamins were given. This agrees essentially with the statement of Joliffe, Wortis and Fein that ophthalmoplegia is invariably preceded or accompanied by peripheral neuropathy in thiamine-deficient patients." R. IRVINE.

PYRUVIC ACID STUDIES IN THE WERNICKE SYNDROME. H. WORTIS, E. BUEDING, M. H. STEIN and N. JOLLIFFE, Arch. Neurol. & Psychiat. **47:** 215 (Feb.) 1942.

The results of the clinical and chemical studies here presented together with the previously reported pathologic observations of Alexander lead the authors to conclude that the Wernicke syndrome is constantly associated with inability to metabolize pyruvic acid properly.

"The ophthalmoplegia responds to thiamine therapy but not to administration of nicotinic acid, riboflavin or pyridoxine. The ophthalmoplegia is invariably preceded or accompanied by acute peripheral symmetric polyneuropathy. Since the latter is almost always associated with thiamine deficiency, this observation supports Alexander's thesis that the two disturbances have a common cause and that the polioencephalopathic changes represent a more complete deficiency of thiamine."

The authors emphasize, however, the fact that, although the Wernicke syndrome is invariably associated with a thiamine deficiency, as seen clinically it does not represent a simple thiamine deficiency. They usually found an additional lack of other nutritive elements. In the treatment of patients with this syndrome they advocate a high calory, vitamin-rich diet with other vitamin concentrates in addition to thiamine.

R. IRVINE.

Ocular Muscles

TWO CASES OF ORTHOPTIC INTEREST. E. B. ALABASTER, C. RUDD and M. TREE, Brit. J. Ophth. **26:** 304 (July) 1942.

The first patient was a boy aged 2 years with left convergent strabismus. Refraction disclosed compound hyperopic astigmatism. Glasses correcting this error were ordered. Four years later there was a deviation of 12 degrees without and of 6 degrees with the glasses. Orthoptic treatment, including occlusion, was carried out from 1935 until 1937, with only slight change. It was then discontinued. In 1941 the Maddox rod test showed 10 prism diopters of esophoria and the Maddox wing test 11 to 15 prism diopters. There was simultaneous macular perception.

The second patient was a man who had had an injury of the supraorbital margin with a fracture of the skull on the right side. Diplopia was present for two days after removal of the bandages. At the time of ophthalmic examination the right eye was displaced downward 1 cm. and there was slight exophthalmos. A roentgenogram showed a fracture of the right malar bone, passing obliquely down and out from the orbital margin, and a fissured fracture in both the roof and the floor of the right orbit, passing directly backward from the orbital margins at the sites of an irregularity already noted on palpation. There were 1 degree of esophoria with no hyperphoria when the patient looked ahead, 6 degrees of esophoria with 10 degrees of right hyperphoria

when the patient looked downward and fixed with either eye and 2 degrees of esophoria with 1 degree of left hyperphoria when the patient looked up and fixed with either eye. The field of diplopia revealed involvement of the superior and the inferior oblique muscles and of the superior and the inferior rectus of the right eye. Despite the muscular anomaly, the patient, who was engaged in airplane engine maintenance, stated that he ordinarily noticed no diplopia, drove a car to and from his work without trouble, occasionally rode a motorcycle and as part of his work did airplane testing in flight, during which he took over the controls. It must be emphasized that this patient had had no orthoptic training at any time and, in spite of the great displacement of his right eye, experienced only a minor degree of diplopia as a temporary phenomenon. Since then he has been proved to possess stereoscopic vision sufficient for him to have adequate control of a motorcycle, a motor car and an airplane in flight.

W. ZENTMAYER.

NYSTAGMUS. E. ADROGUÉ, Arch. de oftal. de Buenos Aires **15:** 167 (April) 1940.

In every case of nystagmus it is essential to have a minute objective and subjective examination, with a notation of the circumstances attending the onset and of all the general, neurologic, ophthalmic and otologic data available, together with supplementary nystagmograms (Ohm) or cinematograms (Adrogué) for determination of the more exact characteristics.

Nystagmus is classified as latent, spontaneous and provoked, positional nystagmus being a variety of the spontaneous.

Gaze is elaborately studied in its origin and development and in its pathways from the voluntary cortical center in the second frontal convolution to the nuclear pontile centers (Dejerine), with the symptoms arising from its interruption or irritation, and its final entrance into the posterior longitudinal fasciculus.

The more important oculomotor reflexes are fixation of points stimulating the retinal periphery and the following of a moving object. In optokinetic nystagmus attention is a factor of the utmost importance, its intensity varying greatly in different persons; it is absent in destruction of Dejerine's corticonuclear pathway. The author refers to indirect connections of the nuclear centers with the occipital, temporal and parietal lobes. All this tends to show that nystagmus may be produced by the most diverse external stimuli and that it cannot be attributed to any single factor.

The investigations, findings and explanations related to the existence of supranuclear centers and their relations and identity with the vestibular nuclei are discussed at length.

Adrogué considers first the spontaneous forms and next those provoked by voluntary movements of gaze, leaving the reflex varieties to the otologist. The time of occurrence and the form of the varieties of spontaneous nystagmus and their combination with vertigo are discussed in connection with vestibular, commissural and cerebral lesions, with lesions of the acoustic and the vestibular nuclei, with postencephalitic syndrome and with other infratentorial lesions.

In connection with nystagmus provoked by voluntary conjugate deviations in the extreme limits of the ocular field (the most frequent clinical variety), the author considers the occurrence of special value diagnostically when unilateral or more pronounced on one side. This form is illustrated by several examples.

From hundreds of observations on patients with cranial hypertension, Adrogué concludes that nystagmus can be found only in association with lesions of the posterior fossa, especially infratentorial, its diagnostic value being greater if it is accompanied by symptoms pointing to lesions in that region.

Resilient nystagmus provoked by ocular movements is frequent and indicates compression of the afferent pathways of the oculomotor nuclei in the posterior longitudinal fasciculus. Cerebellar lesions can provoke resilient nystagmus on the same side.

The author considers that resilient nystagmus provoked by conjugate deviations is a paresis, which would explain its disappearance after a decompressive operation.

C. E. FINLAY.

Retina and Optic Nerve

DETACHMENT OF THE RETINA. R. ARGAÑARAZ, Arch. de oftal de Buenos Aires **16:** 465 (Sept.) 1941.

In detachment of the retina the lesion consists in a cleavage of the primitive layers of the invaginated optic vesicle, the outer pigmented layer remaining firmly attached to the choroid and the inner layer, which comprises the more important visual elements, separating from it, the cleft being occupied by a serous, inflammatory or hemorrhagic exudate. The lesion may be brought about by a variety of factors due to many different pathologic processes.

From an etiologic, a pathogenic and a surgical viewpoint, Argañaraz distinguishes two major types, the idiopathic and the symptomatic. The idiopathic, which is curable surgically and commences with the classic tear of the retina, is due to a retraction of the vitreous and is brought about by myopia, senile degeneration of the retina, chronic torpid choroidal processes and trauma. The symptomatic type is not curable by operation, presents no initial tear and is best explained by choroidal exudation; it comprises separation due to nephritis (albuminuric retinitis), orbital cellulitis, acute cyclitis and tumor.

The different varieties are dealt with in detail. Of the idiopathic type, the author describes a cystoid degeneration and thinning of the retina in the equatorial region, and he considers the eventual detachment as due to retraction of the vitreous, which brings about a tear of the thinned retina. The symptomatic varieties are due to a general disease or to a local inflammatory process, and the detached retina is profoundly degenerated.

Argañaraz next takes up the subjective and the objective symptoms of the idiopathic type, stressing the importance of recognizing and localizing the retinal tear, which most commonly is to be found in a circular equatorial band 5 to 7 mm. wide in the region of the ora serrata. He describes the different forms of tears and his technic for their localization, according to which he uses dilation with epinephrine hydro-

chloride and indirect ophthalmoscopy, and he describes a globe model on which he marks the detachment.

Finally, the different operative procedures (cautery, trephining, perforating and surface diathermy) are taken up. The necessity of an early operation is urged.

C. E. FINLAY.

Tumors

REPORT ON A CASE OF LYMPHOMA OF THE ORBIT. M. L. HINE, Brit. J. Ophth. **26:** 297 (July) 1942.

The patient was a spinster aged 58 years. There was a history of increasing swelling of the left upper lid for five years. Three years previously an exploratory incision into the orbit, with a biopsy, disclosed a growth extending into the orbit. The diagnosis was lipoma. When the patient was seen by Hine there was secondary optic nerve atrophy. Vision amounted to light perception. A roentgenogram showed infiltration of the frontal and ethmoid sinuses. The Wassermann reaction was weakly positive. The biopsy diagnosis was lymphoma. Treatment was by roentgen rays. Eight months later there remained only slight exophthalmos, the ocular movements were good and the orbit was free of the growth.

W. ZENTMAYER.

Vision

THE IMPORTANCE OF NIGHT-VISION TESTS. F. E. PRESTON, Brit. M. J. **1:** 800 (June 27) 1942.

As road accidents are most likely to occur at twilight, the author believes that motorists should be given a test of night vision. The Bishop Harman test, according to the author, will meet all the requirements of the average busy ophthalmologist, and the apparatus can be conveniently installed in the consulting room. Most persons are apt to have an erroneous idea of their visual ability in subdued light. Not only is it important for motorists to be examined for their vision in poor light, but pedestrians should likewise be examined, and the public should realize the value of an assessment of night vision as well as of day vision. Such an assessment could be easily carried out on children by school medical officers.

Finally, the problem of the words "hemeralopia" and "nyctalopia" is taken up. On account of the confusion as to their precise meaning it is suggested that instead of speaking of tests for night blindness the physician should definitely state that the tests are for deficiency or dimness of sight at night, and a much better term to explain this deficiency would be "nyctamauria" or "nyctamauroma."

ARNOLD KNAPP.

Therapeutics

CLINICAL OBSERVATIONS AND DEDUCTIONS IN THE THERAPEUTIC USE OF SULFONAMIDE [SULFANILAMIDE] AND ITS DERIVATIVES IN OPHTHALMOLOGY. J. H. YOUNG, Brit. J. Ophth. **26:** 241 (June) 1942.

The drugs employed were sulfanilamide and azosulfamide (disodium 4-sulfamidophenyl - 2′ - azo - 7′-acetylamino-1′-hydroxynaphthalene-3′,6′-

disulfonate; "prontosil soluble"). Sulfanilamide was used prophylactically before operations for iris prolapse and before intraocular operations. Azosulfamide was employed as an additional safeguard. Therapeutically, it was used in the treatment of nonspecific iritis and iridocyclitis, specific (gonorrheal) iritis and iridocyclitis, prehypopyon ulcer (no cases of hypopyon ulcer have occurred since the introduction of sulfanilamide therapy), cellulitis of the orbit, stitch (abscess) cellulitis, intraocular infection and trachoma. For all traumatic lesions of the conjunctiva and the cornea azosulfamide has no peer. A 2.5 per cent solution meets the need clinically.

The experience gained in the use of local chemotherapy for ocular chemical burns is convincing to the author that azosulfamide will be of incalculable assistance in the treatment of all ocular lesions which may result from chemical warfare. The use of sulfanilamide in the treatment of other lesions resulting from the war will greatly improve the prognosis, not only as to the ultimate cosmetic effect but as to the functional capacity of the eye. There are a number of case reports.

W. ZENTMAYER.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

KAUFMAN SCHLIVEK, M.D., *Chairman*

BRITTAIN PAYNE, M.D., *Secretary*

April 20, 1942

Primary Tuberculosis of the Conjunctiva. DR. OLGA SITCHEVSKA (by invitation).

A boy 18 months old was seen in the ophthalmic clinic of the New York Infirmary for Women and Children in April 1941. He had swelling and drooping of the left upper eyelid and a lump on the left cheek in front of the ear which had been noticed simultaneously five weeks previously.

The conjunctiva of the left upper eyelid was thickened and congested and had a number of follicles of various sizes; some were confluent and proliferating and covered in places by a grayish membrane with a tendency to bleeding. The lacrimal gland was enlarged. The bulbar conjunctiva and the cornea were intact. The face was deformed because of a greatly swollen left preauricular gland, which was soft and fluctuating and about 2.5 by 3 cm. in size. The child was hospitalized. The preauricular gland was aspirated, and tubercle bacilli were found in the smear. A biopsy specimen from the conjunctiva was taken three weeks later, and the histopathologic diagnosis was tuberculosis of the conjunctiva, with typical tubercles and tubercle bacilli in the excised tissue.

The conjunctiva improved rapidly after the biopsy; the suppurated and fistulized preauricular and submaxillary glands were improved by treatment with several small doses of roentgen rays. The child was discharged from the hospital in an improved condition.

Roentgen studies of the lungs of the child and of both parents gave negative results. The possible source of infection was contact with a man who had active pulmonary tuberculosis. The diagnosis of primary tuberculosis of the conjunctiva was made (1) because there was no lesion in any other organ of the body, (2) because the process was unilateral and (3) chiefly because of the involvement of the regional lymph nodes, which according to Ranke's classification is typical.

The age, the incidence, the mode of infection and the clinical types were indicated. Gifford's differential diagnosis of the conjunctivoglandular syndrome of Parinaud's conjunctivitis, namely tuberculosis of the conjunctiva, oculoglandular tularemia and leptothrix, was briefly discussed.

Photographs of the child's face and two photomicrographs illustrated the condition.

DISCUSSION

DR. PHILLIPS THYGESON: I should like to emphasize the rarity of the condition. In Colorado I saw many patients with ocular tuberculosis without seeing any in whom the disease involved the conjunctiva, while in Iowa I saw 1 patient with primary conjunctival tuberculosis and in New York I have seen 1 other patient in consultation. The cases of these 2 patients have paralleled strikingly the case presented here, in that in both the disease was ulcerative in type and the diagnosis easily made by the finding of tubercle bacilli in the ulcers. In both the tuberculosis healed spontaneously without any definite therapy. I think it is worth while to consider ulcerative lesions in the conjunctiva in general. I recall having seen 6 patients with conjunctival ulcers, and of these 1 proved to have tularemia, 2 were tuberculous and an etiologic diagnosis was never made for the other 3.

DR. LOUISE H. MEEKER (by invitation): Dr. Sitchevska was fortunate in finding the bacilli rather easily, both in the tissues and in the smears from the cultures. In the case I wish to illustrate by presenting two lantern slides, there was greater difficulty. This case was scheduled to be reported before the Section of Ophthalmology twenty years ago. The associates of the ophthalmologist who was to present it did not believe the lesion could really be called tuberculosis. We searched a long time but found no bacilli, and we had only three weeks to prove the clinical diagnosis as scheduled on the program. We put tissue in the anterior chamber of a rabbit's eye, and I shall show the result on the two slides. The first slide pictures the lesion seen in the tissue from the conjunctiva, not a definitely tuberculous lesion, although it was promising. Several giant cells of the Langhans type are typical; others are not so clear, and the stroma is also open to question. At the end of three weeks, lesions were seen in both irises of the rabbit. One eye was enucleated, and slide 2 shows a section of the iris. There are early epithelioid cell tubercles, and the whole iris showed the same picture. The other eye was not enucleated. In due time the rabbit died of tuberculous meningitis. This is another method of proving tuberculosis of the conjunctiva.

DR. OLGA SITCHEVSKA: I wish to thank Dr. Thygeson and Dr. Meeker for discussing my paper. I want to point out that in the majority of cases the condition occurs at an early age because the organism has not developed allergy for tuberculosis. The tuberculin test, therefore, will give negative results only if the patient is seen at the early stage of the disease, i. e. from three to seven weeks after its inception. Unfortunately, the patient usually comes after that period, so that the intradermal test gives positive results, as it did in the case reported.

Bilateral Subluxation of Lenses: Needling of Posterior Capsule. DR. JAMES W. SMITH.

The patient, aged 20 when first seen, in 1934, had partial subluxation of both lenses. The maximum acuity was 15/100 in the right eye with a —30.00 D. sphere and 15/50 in the left eye with a —21.00 D. sphere. Three months later the left lens wandered into the anterior chamber. A needling operation, with the patient face downward, was unsuccessful, and the lens returned to the posterior chamber. Prior to

a second operation, the patient was placed in a sitting position and the lens was kept in the anterior chamber after miosis. A generous section of the posterior capsule was made with a knife-needle in the right hand. Two weeks postoperatively, a large mass of cortex dropped out of the contracting lens bag to the retina inferiorly, where it remained unchanged. The final corrected vision with an aphakic lens was 20/50 +.

Seven years later a similar operation involving the posterior capsule was performed on the left lens. The resorption of the cortex, however, was much slower than in the right eye. After maximum clearing of the lens cortex had resulted, it was necessary to perform a de Wecker discission of the capsular remnants. The corrected vision with an aphakic lens was 20/50 +.

DISCUSSION

DR. RALPH I. LLOYD: I examined Dr. Smith's patient and found the details he spoke of. In addition, there was evident thinning of the tapetum, so that the choroidal vessels were more clearly seen, and some of them seemed to show the signs of early sclerosis. There were pigment granules attached to strands of the vitreous. I think the degeneration of the right iris was part of a nutritional condition of which the dislocation of the lens was an expression. I have seen the same condition in a family with arachnodactyly, and it is probable that the patient had only the ocular symptoms but that typical cases could be found in the family. Dr. Smith achieved fine vision with his operations, but I prefer complete removal of the lens rather than needling. Clearing of the lens, while slower after needling of the posterior capsule than after needling of the anterior capsule, is freer from an accompaniment of glaucoma. It is my habit to consider every congenital bilateral dislocation of the lens to be a manifestation of arachnodactyly unless proved otherwise.

DR. WILLIS S. KNIGHTON: I should like to add a case Dr. Lloyd was interested in, that of a man 34 years old who presented himself at the New York Eye and Ear Infirmary one and a half years ago with arachnodactyly and bilateral subluxation of the lenses. He was wearing minus lenses. Somebody had attempted to perform refraction on him through the upper segment of his own crystalline lens. Refraction through the aphakic part of the eye above his crystalline lens gave a result of 20/20 vision. On Dr. Lloyd's advice, the right lens was extracted. After the making of a Graefe cataract incision, a loop was introduced behind the lens. With pressure against the cornea and a rather hard pull on the zonular fibers below, the lens was removed in capsule. There were no complications, and the patient had 20/20 vision afterward. He refused to have an operation on the other eye because he was working, and that lens has remained in place, still subluxated.

Case of Argyrosis of the Cornea. DR. A. J. LANCHNER (by invitation).

This case is presented because it is unusual to see argyrosis of the cornea. The patient was a white American man who had been a silver polisher for fifty years. He first came to the outpatient department of the Brooklyn Eye and Ear Hospital in June 1935, complaining of dimness of vision of both eyes. At this time it was noticed that he had

cataractous changes in both lenses and argyrosis of the conjunctiva in both eyes.

Two years later cataract extraction was performed on the left eye.

Four years later he returned to the Brooklyn Eye and Ear Hospital for removal of a basal cell carcinoma of the skin below the right eye. At that time he was examined with the corneal microscope and the slit lamp. A beautiful picture of argyrosis of the cornea was revealed. There was a silvery mottled effect on Descemet's membrane, which resembled "worm tracks." At the margin it could be seen that the color was really brown, and not silvery. The epithelium and the interstitial tissue of the cornea up to Descemet's membrane were clear. In fact, the contrast between the normal corneal tissue and the mottled Descemet's membrane was so marked that the corneal tissue looked more transparent than it usually does.

DISCUSSION

DR. JOSEPH LO PRESTI (by invitation): The most interesting problem raised by a review of the 357 recorded cases of argyria, or argyrosis, collected by Hill and Pillsbury is the one concerned with the vast difference in the amount of silver responsible for these conditions. This difference as measured in terms of the time in contact (therapeutic or industrial) with silver compounds ranges from a few days to several decades. Undoubtedly, the data of each case cannot long stand critical examination, and it may be that in the cases at both extremes the answer to this phase of the problem may be found in misinformation or in omission of certain facts. However, that there does exist a considerable difference in the quantity of the metal and in the time of contact in carefully studied cases cannot be disputed.

In addition to the obvious effects of inflammation, abrasion and ulceration of the epithelium on absorption, there are other factors almost as important in determining the amount of metal entering the body tissues. The chief routes involved include the gastrointestinal tract, the respiratory tract and the conjunctival sac, besides the intravenous route.

A. Gastrointestinal Tract: Ingested silver compounds change to silver chloride or silver albuminate or are reduced to metallic form to be carried mechanically by white blood cells and other representatives of the reticuloendothelial system. The protein salts formed vary in amount and in stability with the particular p_H prevailing and its relationship to the isoelectric point of the protein in question (for albumins the range runs from p_H 4.7 to p_H 5.4). Double salts of the silver proteinates are formed with chlorides and so further enhance absorption by virtue of their greater solubility.

B. Respiratory Tract: In the upper portions of the tract the process may be similar to that just described, but in the lower reaches, the lungs, the role of the reticuloendothelial system perhaps is dominant.

C. Conjunctival Sac: Once more, similar compounds are probably involved, but in different proportions, depending on the p_H, on the concentration and varieties of proteins and electrolytes and on the amount and type of discharge present and its own p_H (usually acid), mucus content and even physical characteristics.

The transportion of silver within the body, first held to be via the lymphatics, now is believed to be hematogenous. The reticuloendothelial system no doubt plays no small part in this process.

Metallic silver, silver chloride, silver sulfate, silver sulfide, silver stearate, silver mucoproteinate, silver albuminate and unknown silver organic compounds make up the list of forms of silver deposit in the tissues. According to the mechanical theory alluded to previously, the metallic silver is mechanically filtered out by meshes of connective tissue. The chemical theories require the reducing action of light or of the tissue themselves, especially elastic fibers, which, according to Kino, have a specific function in this regard.

Excretion studies are incomplete, but silver sulfide in the stool and perhaps metallic silver in the urine are the two chief forms of the eliminated product.

To summarize, the predisposing factors in the production of argyria can be deduced from the interrelationships of the variables mentioned, thus:

I. Absorption: This may be induced by abnormalities in structure, such as abrasions or stenosis of excretory passages, and abnormalities in physiology, such as inflammation and secretion, the products of which vary in physical and chemical properties, for example in p_H, chloride content and protein content.

II. Transportation: When transportation facilities are embarrassed as by the concomitant administration of other heavy metals (mercury, bismuth) or by dehydration or excessively high blood chloride levels, deposition is favored and excretion diminished.

III. Deposition: Gaul and Staud found that the intensity of the silver line as determined spectroscopically in tissues increases with age. The implication of this finding is self evident. The influence of light and, related to this, the amount of pigment (melanin) render persons more susceptible to the development of argyria.

IV. Excretion: Dysfunction of the lacrimal passages and of the gastrointestinal tract and renal or hepatic damage would cut down on the rate of elimination of the metal.

Pupillographic Studies in Simple Glaucoma: A Preliminary Report.
DR. OTTO LOWENSTEIN and DR. MARK J. SCHOENBERG.

A short review of the principles of pupillographic methods of studying the pupillary movements and a report on pupillary disturbances in cases of noncongestive glaucoma was presented. Some of these disturbances are as follows: 1. The latency period, preceding the pupillary contraction, is prolonged. 2. The psychosensory restitution phenomenon is diminished. 3. The reaction to darkness stimulation is abnormal. 4. Signs of pupillary fatigue appear early. The pupillographic findings indicate that the pupillary disturbances observed in our cases of glaucoma are of central origin.

DISCUSSION

DR. ISADORE GIVNER: Granting that the report of Dr. Schoenberg and Dr. Lowenstein is a preliminary one, I believe they are to be congratulated on this paper in that they have opened up a great many

new paths of thought in the whole conception of glaucoma. It makes one look for the causation of glaucoma not locally in the eye but farther back in the brain, bringing to mind Elwyn's contribution on this subject. I had an opportunity to study 9 cases of glaucoma with pupillography, and I should like to show one slide to bring out a few points. The latency period before contraction to light should not be longer than 0.27 second normally. The latency period for dilation should not be above 0.35 second. The patients with glaucoma whom Dr. Schoenberg spoke about showed these characteristic features: a prolonged latency period for pupillary contraction to light, a sluggish reaction to light, a prolonged latency period for dilation and a sluggish dilation. The patients he studied had not had drops in their eyes for three days or longer. The patients I sent to Dr. Lowenstein had had drops in their eyes the night before, so that they had had drops anywhere from eight to thirty hours previous to the pupillographic studies.

One is taught that the action of pilocarpine lasts about six hours and the action of physostigmine twelve hours. Here one sees pupillographically that even after thirty hours the depth of contraction is much smaller than without a miotic. (A slide was shown.) Another point of interest is that the characteristic features of glaucoma as shown in Dr. Schoenberg's case were present in my cases but in a much reduced scale. My patients, too, had a long latency period for contraction, a sluggish reaction to light, a long latency period for dilation and a sluggish reaction for dilatation. This is interesting, because one sees that in spite of the fact that the tension was reduced they showed the characteristics which the patients with glaucoma showed without miotics. It would appear that the pupillographic changes are not dependent on increased intraocular tension alone.

Another point showing how pupillography may possibly be of aid in diagnosis is seen in this graph. (A slide was shown.) In a clinic I saw a patient who had been under treatment for a year for glaucoma. Looking over the case history and the ocular findings, I saw no reason for this diagnosis. There was never an increase of tension, nor were there changes in the field. Without telling Dr. Lowenstein any diagnosis, I sent the patient for pupillographic study. The graph shows a prompt reaction to light, such as is not seen in cases of glaucoma, and so Dr. Lowenstein wrote me he felt that the case was not one of glaucoma.

One cannot expect to know much about pupillography as applied to the study of glaucoma when so few cases have been studied, but I feel that this report does open up a great many new fields of thought, and for this reason pupillography should be encouraged.

Dr. Percy Fridenberg: May I add a few generalizations suggested by this interesting paper? Dr. Lowenstein's study is a study in pupillary fatigue and its various phases, and Dr. Schoenberg has interestingly brought out the connection of this fatigue with glaucoma. It will be noticed that the seven stages he has mentioned are exactly the same as those produced by repeated stimuli, changes which have to do with time, that is with speed or sluggishness of reaction, and with space, expressed in amplitude of pupillary changes, and it struck me that these authors might well summarize their findings and tell what these glaucomatous changes mean in terms of pupillary effect. Are they not an

expression of a pathologic fatigue of the pupil similar to the physiologic fatigue due to repeated stimuli? Dr. Givner, too, suggested that there must be something in addition to increased tension; whether this is repeated stimuli of the vegetative nervous system or something else I do not know.

The question was raised why the pupil has such a complicated representation of cerebral centers, nuclei and so on, and it seems to me strange to claim that the pupil is not directly concerned with vital processes. I think it is. It is known that the muscle of the iris is so closely related to that of the heart that drugs are tested in the laboratory by their reactions on the pupil, and it is known by their reactions on the pupil how they will act on the heart, either to accelerate it or to slow it. It would be interesting to know whether there was any cardiac response in the fatigue experiments described. But one comes back to the question why the pupil is so vitally important. The defense mechanism of fight or flight—and this goes back to phylogenesis of earliest times—depends almost entirely on visual stimuli, and the pupillary reaction is not just a response; it is an indication and consequently a warning and also a sign that the heart and the endocrine glands have gone through a certain phase, and the result is to produce either fight or flight, and that influences the heart reaction. The pupillary reaction is merely an indication that the whole system has been affected (cf. Cannon, on the secretogenic origin of the emotions).

Dr. Benjamin Friedman: I should like to point out one or two facts in the physiology of the eye and to ask Dr. Schoenberg and Dr. Lowenstein to correlate them with the findings reported in their paper. The first is that fatigability of nerve fibers apparently does not exist. I know of no experiments which indicate that a nerve fiber is susceptible to fatigue; are not the pupillographic fatigue curves which were shown applicable only to the muscle of the iris and not to the nerves which supply the iris?

The second fact relates to the electric action currents which are taken off the optic nerve when the retina is stimulated. When darkness is used as a stimulus the fibers of the optic nerve do not remain dead to electric currents, but they show a response to the darkness, and I should like to ask whether the portion of the pupillographic curve which is recorded in darkness is not a reaction from specialized receptor cells in the retina.

Lastly, in studies of the chronaxia, or the sensitivity of the retina to electric stimuli, superimposed sounds have been shown to have a variable effect on the sensitivity of the retina. The irritability of the vestibular mechanism also seems to play a role. Is it possible to relate such findings with the effects of acoustic stimuli on the pupillographic curve?

Dr. Otto Lowenstein: Dr. Givner's findings point to the necessity of further pharmacodynamic studies of glaucoma by means of pupillography.

I fully agree with Dr. Fridenberg on the importance of the mechanism of the pupils and its relation to other mechanisms of the autonomic nervous system—such as the heart—which are directly concerned with vital processes. These mechanisms all are possibly part of the defense

mechanism of fight or flight. If the symptoms of glaucoma are something in addition to increased tension and if they really depend in part primarily on central nervous processes, it is not surprising to find that they are similar to the symptoms of physiologic fatigue. The course of fatigue runs through seven well developed stages, and this "law of fatigue" governs the fatigue process of the pupil. It is of great importance for pathology, for one finds in cases of disintegrating function (cases of neurosyphilis, for instance) that the reaction types of those seven stages, which are transitory in cases of physiologic fatigue, exist as more or less permanent or fixed types of reaction in the first response to light (without preceding fatigue). I call these phenomena the "law of analogy" between physiologic fatigue and pathologically disintegrating function. They are, of course, an expression of a pathologic fatigue of the pupil and may be based on lesions of the pathways of nervous control of the pupil (Lowenstein, O.: Der Psychische Restitutionseffect, Basel, Benno Schwabe & Co., 1937. Löwenstein, O., Friedman, E. D.: ARCH. OPHTH. **27**:969-993 [May] 1942.)

As to the question of Dr. Friedman, I should like to point out that the question of whether nerves fatigue has long occupied neurologists and physiologists. For medullated nerves, F. W. Fröhlich (*Ztschr. f. allg. Physiol.* **3**:468, 1904) was the first to mention fatigue symptoms. His discoveries were confirmed by numerous other authors, and today it is the generally accepted view (Broemser, P., in Bethe, A.; Von Bergmann, G.; Embden, G., and Ellinger, A.: *Handbuch der normalen und pathologischen. Physiologie,* Berlin, Julius Springer, 1930, vol. 9, p. 222) that medullated nerves are doubtless fatigable, but much less so than muscles. Symptoms of fatigue are a decrease of irritability, a decrease of conducting capacity, an increase in the latency period and a modification of the action current, all of which are easily observed in states of low temperature, in suffocation and in narcosis. I could show that autonomic nerves, and particularly autonomic reflexes, are fatigable and that the symptoms of fatigue are similar to those of the nonmedullated nerves. I was able to show further that a regulation mechanism exists by which the fatigued nerves continuously recover. I called this mechanism the psychosensory restitution phenomenon. It concerns the whole nervous system and all functions regulated by the autonomous nervous system, which means that it regulates the state and the activity of all tissues, including the retinal functions. It explains the effect of superimposed sounds on the sensitivity of the retina in experiments with chronaxia. The pupillary reaction to darkness is a reflex independent of the reflex to light. The pathways of its nervous control are different from those of the reflex to light (Lowenstein and Friedman).

In conclusion, I wish to emphasize once more that a great number of pupillographic findings in cases of glaucoma suggest that they are, at least partly, primarily due to a condition of the central nervous system. In our cases these pupillary symptoms could be detected in both eyes, even when, clinically, the symptoms of glaucoma were only unilateral. The number of our cases, however, is not great enough to allow a generalization as to these findings. We are able only to suggest certain tendencies as to causation and localization.

Use-Abuse Theory of the Changes in Refraction Versus Biologic Theory. Dr. E. V. L. Brown, Chicago.

This paper was published in full in the November issue of the Archives, page 845.

DISCUSSION

Dr. Willis S. Knighton: The study of the development of the refractive states has long suffered from misconceptions and from the elaboration of theories before all the facts are known. Although this state of affairs is gradually being cleared up, a complete understanding of the subject is still a long way off.

In the present and in past communications, Dr. Brown has made a decided contribution to the facts in the case. His large series of patients who have been followed individually through so many years is unique because it shows the absolute changes that have occurred during those years. Other investigators have usually been satisfied to compare the different refractive states in different age groups, but this proceeding is not so accurate. Individual variations must be taken into consideration, regardless of their conformity or nonconformity to preconceived ideas, or the final refraction curve becomes nothing more than a complacent gross average that explains nothing. Dr. Brown is to be congratulated on his painstaking work. It is especially refreshing to hear that he does not try to develop a new theory. But whoever does theorize must be able to explain the increase in hyperopia that continued up to the age of 7 in Dr. Brown's cases. That is a fact that must fit in.

Ophthalmologists are getting away from the mechanistic, or "use-abuse," theory to explain refractive changes. As Dr. Brown pointed out, that theory emphasizes the increase of refraction, the decrease in hyperopia or the increase in myopia. It does not consider the development of hyperopia. If it is carried to an absurd conclusion, it would seem to indicate that, since weakening influences cause a lessening of the hyperopia, emmetropia itself is not so desirable as hyperopia.

One of the greatest stumbling blocks in the consideration of refractive states has been the idea that emmetropia is a fixed ideal and that any deviation is abnormal. Today the conception of refractive states is more comprehensive, and emmetropia is considered merely a point on a scale of values.

The depth of the anterior chamber, the thickness of the lens, the radius of curvature of each surface of the lens, the refractive power of the cornea, the refractive power of the lens, the refractive power of the eye, the length of the axis—all these vary according to the laws of normal variability, and yet all must be combined to show the refractive state of an eye. Emmetropia cannot be considered a fixed quantity when it occurs as the result of such variations as those shown in the following tabulation (Trön):

	Refractive Power of Eye, D.	Length of Axis, Mm.
Emmetropia	52.59 — 64.21	22.42 — 27.30
Myopia	53.84 — 66.88	22.19 — 38.08
Hyperopia	53.31 — 65.30	20.75 — 25.62

It will be noticed that neither the refractive power alone nor the length of the axis alone determines the refractive state. Furthermore,

a refractive power of 53.84 to 64.21 D. is common to emmetropia, hyperopia and myopia. The length of the axis likewise may vary within considerable limits and still remain normal for any refractive state.

The next tabulation (Trön) shows the effect of different combinations of these variables:

Emmetropia			Ametropia		
	Refractive Power of Eye, D.	Length of Axis, Mm.		Refractive Power of Eye, D.	Length of Axis, Mm.
	62.31	23.11	—3.5	62.21	24.25
	55.77	25.62	—5.0	60.90	25.60
	62.02	23.38	+4.0	57.72	23.46

In the second case of ametropia a myopia of 5 D. is combined with a refractive power of 60.90 D. and an axial length of 25.60 mm. The case cannot be considered one of axial myopia, because the axial length is the same as that in the adjacent case of emmetropia. Neither can it be regarded as a case of refractive myopia, because the refractive power is also within the emmetropic range. The same argument holds in some cases of hyperopia, and such effects of different combinations have been called "combination ametropia" by Trön.

It is surprising, in view of the possible combinations of these variables, that the refractive changes with age are so consistent and adhere so closely to a theoretically derived binomial curve. That they do would seem to indicate a degree of freedom from external causes, the mechanistic theory, and a conformity to physiologic processes, the biologic theory.

Even when there are racial differences and the refraction goes from hyperopia to myopia, the form of the curve is the same; it is merely shifted toward the myopic side.

In cases of extreme hyperopia or myopia the changes do not follow this theoretic curve, but in these instances other variable factors have been introduced. That these variables work separately is shown by the fact that high myopia can exist without fundus lesions and that fundus lesions can be found in association with myopia of low degree. This fact is explained by assuming that axial length and fundus lesions are dissociated phenomena which are usually, but not necessarily, coupled genetically. High refractive errors are believed to be inherited recessively, whereas small errors are dominant in their transmission.

With all of this emphasis on the biologic theory, it has been necessary to modify the earlier conceptions of undue influences from mechanical causes. Yet it would be unwise to insist that all refractive changes are predetermined and not susceptible to later external influences. Reports of the increase or decrease of myopia, for example, from different countries are so conflicting that one must wait until more facts are available.

Statistics of the sort presented by Dr. Brown are significant. They do not prove anything except that they exist, but in that very fact they fill in part of the picture and demand recognition in any and all explanations of refractive changes.

Book Reviews

Binocular Imbalance. By Margaret Dobson, M.D. Cloth bound. Pp. 96, with 19 illustrations. London: H. K. Lewis & Company, 1942.

In this volume the author "has endeavored to show how a correct relationship between the relative amplitudes of convergence and accommodation can be obtained." It is divided into fifteen short chapters and an index. It opens with an elementary discussion on binocular vision and the extraocular muscles. In the following chapter, on convergence, one finds the statement that "all lateral imbalances are errors of convergence and all tests are convergence tests," yet later, in the chapter on esophoria, the diagnostic features of divergence insufficiency are outlined. Even though the author does believe that no active divergence is possible, such apparently conflicting statements are confusing to the beginner. The principles of retinoscopy, both static and dynamic, are clearly outlined. The treatment of the various types of heterophoria is given, with special emphasis on the value of stereoscopic training. The concluding chapter is a general survey of the author's opinions on the subject, which on the whole conform with the generally accepted views.

There is little to recommend this volume. It is elementary yet confusing and lacks the clearness of style so necessary in such a treatise.

JOHN H. DUNNINGTON, M.D.

Occupational Tumors and Allied Diseases. By W. C. Hueper, M.D. Price, $8.00. Pp. 896. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

In this stately volume, which covers the widespread subject of occupational tumors and allied diseases in many fields of medicine, the chapter on the eye and its adnexa is necessarily brief. In the four pages that are devoted to it, however, a great amount of valuable information is collected. Chemical agents (arsenic, tar, pitch, oils and paraffin) and physical noxae (solar and ultraviolet rays, roentgen rays and radioactive substances) as well as physical trauma are considered in their relation to tumors of the eye. The controversial observations and their interpretation in ophthalmologic literature, especially in regard to trauma and melanosarcoma of the uvea, are dealt with cautiously, and the divergent opinions are given.

It is of practical value to find the scattered literature on this topic concisely and well presented. In addition, there is much applicable to the eye in several parts of the book, as, for instance, in the introduction on the concept and significance of occupational tumors and in the chapters on occupational and accidental tumors of the skin, of the mesenchymatous tissue and of the nervous system. The final chapters, on special aspects of occupational tumors, the relation of occupational neoplasia to the theories of cancerigenesis and the medicolegal and public health aspects, round and deepen the knowledge of the readers who want to use the work for more than reference.

LUDWIG VON SALLMANN.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Consolacao, São Paulo, Brazil.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

President: Dr. C. H. Chou. 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. I. Iwre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Mária-utca 39, Budapest.
All corespondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.

PALESTINE OPHTHALMOLOGICAL SOCIETY

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

POLISH OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Dr. A. J. Ballantyne, 11 Sadyford Pl., Glosgow, C. 3, Scotland.
Secretary: Dr. C. Dee Shapland, 15 Devonshire Pl., London, W. 1, England.

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President: Dr. Jacques Tupinambo, 258 Inglezes, São Paulo, Brazil.
Secretary: Dr. Silvio de Almeido Toledo, Enfermaria Santa Luzia, Santa Casa de Misericordia, Cezario Motta St.—112, São Paulo, Brazil.

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November. inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

Société Française d'Ophthalmologie

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

Society of Swedish Ophthalmologists

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

Tel Aviv Ophthalmological Society

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

American Medical Association, Scientific Assembly, Section on Ophthalmology

Chairman: Dr. Conrad Berens, 35 E. 70th St., New York City.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.

American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology

President: Dr. Ralph I. Lloyd, 14–8th Ave., Brooklyn.
President-Elect: Dr. James A. Babbitt, 1912 Spruce St., Philadelphia.
Executive Secretary-Treasurer: Dr. William L. Benedict, 101—1st Ave. Bldg., Rochester, Minn.

American Ophthalmological Society

President: Dr. Hunter H. McGuire, 105 N. Braddock St., Winchester, Va.
Secretary-Treasurer: Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y.
Place: Hot Springs, Va. Time: June 1943.

Association for Research in Ophthalmology, Inc.

Chairman: Dr. John Evans, 23 Schermerhorn St., Brooklyn.
Secretary-Treasurer: Dr. C. S. O'Brien, University Hospital, Iowa City.

Canadian Medical Association, Section on Ophthalmology

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

Canadian Ophthalmological Society

President: Dr. Colin A. Campbell, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St., W., Montreal.

National Society for the Prevention of Blindness

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

Academy of Medicine of Northern New Jersey, Section on Eye, Ear, Nose and Throat

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

Central Wisconsin Society of Ophthalmology and Otolaryngology

President: Dr. D. G. Hugo, 130 Main St., Oshkosh.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. Harry C. Messinger, 210 Angell St., Providence, R. I.
Secretary-Treasurer: Dr. Merrill J. King, 82 Commonwealth Ave., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, Time: 8 p. m. third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. Ralph A. Fenton, 1020 S. W. Taylor St., Portland, Ore.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Spencer S. Howe, 103 E. Holly St., Bellingham, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 419 Stimson Bldg., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. M. Kessler, 311 Center Ave., Bay City, Mich.
Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Davis, 1615 Howard St., Omaha.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. L. Chester McHenry, Medical Arts Bldg., Oklahoma City.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.
Place: Richmond, Va. Time: November 1942.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.
Place: Albuquerque, N. Mex. Time: November 1942.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. C. H. Bailey, 29 S. Oakland Ave., Sharon.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. R. R. Kirkpatrick, 6th and Walnut Sts., Texarkana, Ark.
Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. Edward N. DeWitt, 836 Myrtle Ave., Bridgeport.
Secretary-Treasurer: Dr. Henry L. Birge, 179 Allyn St., Hartford

Eye, Ear, Nose and Throat Club of Georgia

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117-3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Lousiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmology and Otolaryngology

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William J. Marshall, 335 Owen St., Missoula.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. G. A. Larson, 114 Roberts St., Fargo.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Ferguson, Second National Bldg., Akron, Ohio.
Secretary-Treasurer: Dr. D. F. Mathias, First Central Tower, Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month, from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. William B. Agan, 1 Nevins St., Brooklyn.
Secretary-Treasurer: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Meyer H. Riwchun, 367 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Sanford Gifford, 720 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. W. J. Abbott, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. L. V. Johnson, 2065 Adelbert Rd., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. William A. Stoutenborough, 21 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. D. G. Sanor, 206 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. Abell Hardin, Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Harvey E. Dowling, 2414 Eaton Tower, Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. James M. Dunn, 1352 Union St., Schenectady.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians

President: Dr. James E. Landis, 232 N. 6th St., Reading.
Secretary-Treasurer: Dr. Sterling F. Mengel, 612 W. Market St., Pottsville.
Time: Last week in April each year.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Felician J. Slataper, 1110-1111 Medical Arts Bldg., Houston, Texas.
Secretary: Dr. Theo. L. Holland, 611 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. John Osburn, 523 W. 6th St., Los Angeles.
Secretary-Treasurer: Dr. Colby Hall, 1136 W. 6th St., Los Angeles.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John W. Truitt, 161 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wiess, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Kaufman Schlivek, 1016–5th Ave., New York.
Secretary: Dr. Brittain Payne, 896 Madison Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. Isidore Givner, 108 E. 66th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Leo P. Coakley, 918 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLGICAL SOCIETY

President: Dr. Hunter H. Turner, 717 Liberty Ave., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Solon L. Rhode, 238 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester. N. Y.

St. Louis Ophthalmic Society

President: Dr. Leslie C. Drews, 508 N. Grand Blvd., St. Louis.
Secretary: Dr. H. Rommel Hildreth, 823 Metropolitan Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting, 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas,
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Louis A. Parsell, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. Robert L. Pohl, 407 Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. Roy Seeley Moore, 1704 State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. John D. Skow, 2001 Collingwood Blvd., Toledo, Ohio.
Secretary: Dr. S. H. Patterson, 125–15th Ave., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. L. Conner Moss, 3260 Wilson Blvd., Arlington, Va.
Secretary-Treasurer: Dr. Harold R. Downey, 1740 M St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.

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